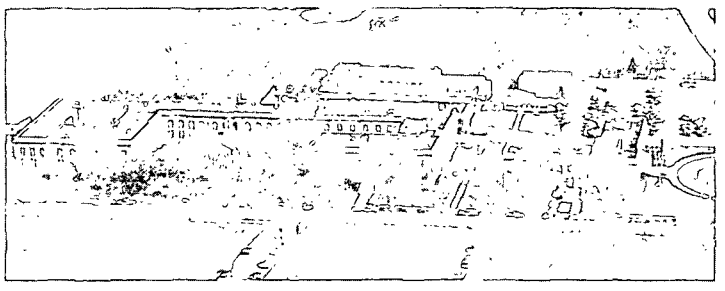

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KOENIGS-KNORR REACTIONS.
I, II, III

JERRY E. WALLACE AND LELAND R. SCHROEDER

MARCH, 1976

Koenigs-Knorr Reactions

Part I. Effects of a 2-O-Acetyl Substituent, the Promoter, and the Alcohol Concentration on the Stereoselectivity of 1,2-cis-D-Glucopyranosyl Bromide Reactions.

Part II. A Mechanistic Study of Mercuric Cyanide-Promoted Reactions of 2,3,4,6-Tetra-O-methyl-α-D-glucopyranosyl Bromide with Cyclohexanol in Benzene-Nitromethane.

Part III. A Mechanistic Study of Mercuric Cyanide-Promoted Reactions of 2-O-Acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl Bromide with Cyclohexanol in Benzene-Nitromethane.

Jerry E. Wallace and Leland R. Schroeder

FORWARD

Synthetic oligosacchardies (glycosides), which are short-chain polysaccharides, have been useful in structural investigations of naturally-occurring polysaccharides. In addition, simple glycosides and oligosaccharides are frequently employed as model compounds for investigations related to the chemical and physical properties of polysaccharides and, in some areas, studies of this type form the only basis for what we presume to know about the polysaccharides. On occasion, these investigations have been thwarted or seriously hampered because of the inability to synthesize the requisite oligosaccharide.

The Koenigs-Knorr reaction is one of a limited number of methods of synthesizing glycosides and oligosaccharides. Thus, attempts are being made to understand the factors which control the products of this type of reaction.

The first paper in this series describes the results of student research in the Special Study program in which the effects of three major variables on the stereochemistry of the Koenigs-Knorr reaction were investigated.

The second and third papers describe the results of Doctoral Thesis research in which the mechanisms of Koenigs-Knorr reactions of glucosyl bromides with "nonparticipating" and "participating" substituents, respectively, were investigated in detail.

The papers will be submitted for publication in the Journal of the Chemical Society.

Koenigs-Knorr Reactions: Part I. Effects of a 2-O-Acetyl Substituent, the Promotor, and the Alcohol Concentration on the Stereoselectivity of 1,2-cis-Glucopyranosyl Bromide Reactions

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ABSTRACT

Koenigs-Knorr reactions of 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide and the 2-O-acetyl analog with cyclohexanol, employing various promoters in the customary reaction solvents, were investigated at 23°C. The promoters employed were Ag_2O with I_2 in chloroform, HgO with $HgBr_2$ in chloroform, $CdCO_3$ in toluene, and $Hg(CN)_2$ in benzene-nitromethane (1:1, vol). Primary emphasis was on reactions having an alcohol (ROH) to glucosyl halide (RBr) molar ratio of 3:1 at a glucosyl halide concentration of ca. 6.5×10^{-2}M. In addition, $Hg(CN)_2$-promoted reactions employing 10:1 and 30:1 molar ratios of ROH to RBr were studied. The 2-O-acetyl-glucosyl bromide selectively formed the β-glucoside (95-98% of the glucosidic products) in all the reactions. In contrast, reactions of the 2-O-methyl-glucosyl bromide were less selective (53-91% β-glucoside), and the selectivity was dependent on the promoter and the alcohol concentration employed. The selectivity for β-glucoside formation was greatest in the Ag_2O system and least in the $CdCO_3$ system. In the $Hg(CN)_2$ system, selectivity for β-glucoside formation increased as the alcohol concentration was increased.

INTRODUCTION

The Koenigs-Knorr reaction[1], in which a substituted glycosyl halide reacts with an alcohol, phenol, or substituted glycose has been employed successfully for the preparation of numerous glycosides and oligosaccharides[2-7]. However, the usefulness of this method has been limited because of the lack of steric control over the reaction. The primary reason for this is the complex way in which the steric course of the reaction is influenced by various factors[8], including, in addition to the configuration of the glycosyl halide, the nature of the C-2 substituent of the glycosyl halide, the alcohol concentration, and the promoter ("acid acceptor"). The purpose of this investigation was to determine the effect of a C-2 O-acetyl substituent, the alcohol concentration, and the promoter system on the stereoselectivity of 1,2-cis-glucopyranosyl bromide reactions. To this end, reactions of 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide (I) and 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide (II) with cyclohexanol employing various promoters in the customary reaction solvents were investigated at 23°C. The promoter and solvent systems employed were: silver oxide-iodine[5] in chloroform, mercuric oxide-mercuric bromide[9] in chloroform, mercuric cyanide[6] in benzene-nitromethane (1:1, vol), and cadmium carbonate[10] in toluene.

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RESULTS AND DISCUSSION

The analyses of the glucosidic products from the reactions conducted in this investigation are presented in the Table. It is noteworthy that all of the reactions of 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide (I) occurred with a high degree of stereoselectivity; the mole fraction of β-anomer (n_β) in the glucosidic products was 0.95-0.98. In contrast, reactions of 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide (II) occurred with lower and varied degrees of selectivity; n_β ranged from 0.53 to 0.91. The selectivity of the 2-O-methyl-glucosyl bromide (II) reactions was extremely dependent on both promoter system and the alcohol concentration employed. These data indicate that the effect of a 2-O-acetyl substituent is more dominant than the effect of either the promoter or the alcohol concentration in reactions of 1,2-cis-glucopyranosyl bromides.

These results are consistent with those of earlier investigations which have shown that reactions of 1,2-cis-glycosyl halides having a 2-O-acyl substituent generally occur with a high degree of inversion at C-1[2,5,11], whereas the stereoselectivity of reactions of 1,2-cis-glycosyl halides having a "nonparticipating" C-2 substituent is extremely variable[12-14]. It has been postulated that the effect of a 2-O-acyl substituent on the stereoselectivity of 1,2-cis-glycosyl halide reactions is due to direct participation of the substituent through formation of a relatively stable 1,2-acyloxonium ion, e.g. (III), which guides the incoming nucleophile into the 1,2-trans position[11]. However, evidence against reaction of the nucleophile at the anomeric carbon atom of the 1,2-acetoxonium ion of 3,4,6-tri-O-methyl-α-D-glucopyranose (III) being very important has been obtained for both hydrolyses[15] and alcoholyses[16,17] of 1,2-O-(1-alkoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranoses (IV and V), even though (III) is an important intermediate in the reaction systems. Another

potential explanation for the high degree of stereoselectivity of the 2-O-acetyl-glucosyl bromide (I) reactions is that the intermediate acetoxonium ion (III) reacts with the cyclohexanol to form the orthoester (VI). Even though the reaction mechanism may be uncertain, it is known that 1,2-(alkyl orthoacetates) of D-glucose can selectively form the alkyl 2-O-acetyl-β-D-glucopyranoside[18]. Thus, if the reaction system contains weak acids, such as HCN in the $Hg(CN)_2$-promoted reaction or H_2CO_3 in the $CdCO_3$-promoted reaction, or if neutralization of the HBr generated in the system is not sufficiently rapid, the orthoester (VI) could be formed and subsequently generate the β-glucoside.

The lower yields of glucosides observed in the Ag_2O- and HgO-promoted reactions may have been due, in part, to hydrolysis. If desiccation is not rapid and efficient, water produced by neutralization of the HBr by Ag_2O or HgO could compete with the alcohol for the glucosyl bromide (and orthoester[15]) resulting in formation of reducing sugars rather than the preferred glucosides. In addition, the yield of glucosides was significantly lower for the Ag_2O- and HgO-promoted reactions of the 2-O-acetyl-glucosyl bromide (I) than for the analogous reactions of the 2-O-methyl-glucosyl bromide (II). This may be indicative of the formation, and partial stabilization, of the orthoester (VI) in the reaction of (I). The analytical procedure did not include analysis of (VI) which would not be stable to direct g.l.c. analysis[15]. A substantial amount of an orthoester has been isolated from a reaction of a 1,2-cis-O-acetyl-glucosyl bromide with a secondary alcohol promoted by mercuric bromide and mercuric oxide in similar solvents[19]. Thus, it is possible that HgO, and potentially Ag_2O[20], may have partially stabilized any orthoester (VI) formed in the 2-O-acetyl-glucosyl bromide (I) reaction, and thereby lowered the yield of glucosides.

Formation of the α-glucoside from the 2-O-methyl-glucosyl bromide (II) is only possible if the bromine atom is not present to shield the α-side of the anomeric carbon atom. Therefore, the formation of cyclohexyl 2,3,4,6-tetra-O-methyl-α-D-glucopyranoside (VII) from (II) is indicative of either bromide exchange to form the β-glucosyl bromide or formation of a carbonium ion. Since the promoters used in this investigation should act as anion-acceptors, the extent of ion exchange should be minimal, and formation of the α-glucoside (VII) should be primarily indicative of carbonium ion formation.

Previous investigations have shown that the promoter may influence the stereoselectivity of a Koenigs-Knorr reaction. For example, reactions conducted in the presence of silver salts have generally been found to be stereoselective, while the results of those employing mercuric salts have been varied[6,7]. The data in the Table show that the stereoselectivity of the 2-O-methyl-glucosyl bromide (II) reactions were significantly dependent on the promoter system. The mole fraction of β-anomer in the glucosidic products (n_β) ranged from 0.91 for the silver oxide-facilitated reaction to 0.53 for the cadmium carbonate-facilitated reaction. The influence of the promoter system is complex and may be due to the nature of the promoter[21], the solvent employed, or a combination of both[22]. Under the conditions of the present study, the stereoselectivity decreased as a function of the promoter system in the following order:

$$Ag_2O > HgBr_2\text{-}HgO > Hg(CN)_2 > CdCO_3$$

The effect of the alcohol concentration on the stereoselectivity of the mercuric cyanide-promoted reactions of both glucosyl halides was investigated (Table). There was no apparent dependence of the glucoside configuration on the alcohol concentration for reactions of the 2-O-acetyl-glucosyl bromide (I). However, for reactions of the 2-O-methyl-glucosyl bromide (II), the mole fraction

of β-anomer in the glucosidic products (n_β) increased from 0.71 to 0.88 as the cyclohexanol concentration was increased tenfold. The dependence on the cyclohexanol concentration indicates that the intermediate glucopyranosyl carboxonium ion was partially shielded by the departing anion, or that the ions existed as an ion pair. As the alcohol concentration was increased, the probability that a nucleophilic substitution would occur before the anion had time to completely dissociate from the carbonium ion increased because the availability of the alcohol to react with the carbonium ion increased. Thus, the relative importance of shielding of the α-side of the carbonium ion increased as the alcohol concentration increased, and resulted in an increase in the selectivity of the 2-O-methyl-glucosyl bromide (II) reactions for β-glucoside formation.

EXPERIMENTAL

Analytical Methods — M.p.s were determined on a Thomas Hoover capillary apparatus which was calibrated against known compounds. Polarimetric measurements were made on a Perkin-Elmer 141 MC polarimeter. Elemental analyses were performed by Chemalytics, Inc. P.m.r. spectra were determined with a Varian A-60A spectrometer at normal probe temperature employing tetramethylsilane as the internal standard in $CDCl_3$ solutions. T.l.c. was performed on microscope slides coated with silica gel G utilizing methanolic sulfuric acid (5:1, wt) spray with charring for component detection.

G.l.c. analyses were performed on a Varian Aerograph 1200-1 instrument equipped with a hydrogen flame ionization detector and a Honeywell Electronic 16 recorder with a Disc integrator. Analyses were performed with: (A) 20% carbowax 20M TPA on 60-80 mesh HMDS Chromosorb W (5 ft x 0.125 in o.d. stainless steel column); column, 155°C; N_2, 21 ml min^{-1}; injector, 205°C; and detector, 265°C; and (B) 5% SE-30 on 60-80 mesh Chromosorb W (10 ft x 0.125 in o.d. stainless steel column); column, 160° → 220°C at 1° min^{-1}; N_2, 16 ml min^{-1}; injector, 205°C; and detector, 265°C.

2-O-Acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl Bromide (I) — 1,2-Di-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranose[15] (7.0 g) was stirred with 1,2-dichloroethane (220 ml) saturated with HBr (15.5 g) for 8 min, and poured into rapidly-stirred ice water. After 10 min, the solution was extracted with chloroform (3 x 100 ml). The extracts were washed with saturated $NaHCO_3$ and water, dried ($CaCl_2$), and concentrated in vacuo to yield (I), pure by t.l.c. (isopropyl ether) and p.m.r. analysis, as a sirup (6.7 g, 91%); $[\alpha]_D$ + 250° (c 1.0, $CHCl_3$); δ ($CDCl_3$) 6.65 (1H, d, $J_{1,2}$ 4.0 Hz, H-1), 4.65 (1H, m, $J_{2,3}$ ca. 9 Hz, H-2), and 2.15 p.p.m. (3H, s, OAc). The large positive specific optical rotation, the small value of $J_{1,2}$, and the low field position of H-1 are indicative of the α-configuration of (I).

2,3,4,6-Tetra-O-methyl-α-D-glucopyranosyl Bromide (II) — 1-O-Acetyl-2,3,4,6-tetra-O-methyl-D-glucopyranose[23] (7.0 g) was treated with HBr in dichloroethane as described for the preparation of (I). Pure (II), as determined by t.l.c. (benzene-ethyl acetate; 1:1, vol) and p.m.r. analyses, was obtained as a sirup (6.1 g, 86%); $[\alpha]_D$ + 244° (c 1.1, $CHCl_3$); δ ($CDCl_3$) 6.58 p.p.m. (1H, d, $J_{1,2}$ 3.5 Hz, H-1). The large positive specific optical rotation, the small value of $J_{1,2}$, and the low field position of H-1 are indicative of the α-configuration of (II).

Cyclohexyl 2,3,4,6-Tetra-O-methyl-α-D-glucopyranoside (VII) — Cyclohexyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside[24] (5.0 g) was deacetylated with methanolic sodium methoxide[25], and methylated in N,N-dimethylformamide (50 ml) with methyl iodide (15 ml) and silver oxide (25 g)[26] to yield (VII) as a sirup (3.5 g, 95%). The sirup was purified by distillation under reduced pressure (0.05 mm Hg) through a 10-cm Vigreux column. The distillate had $[\alpha]_D$ + 148° (c 1.0, $CHCl_3$), δ ($CDCl_3$) 5.06 p.p.m. (1H, d, $J_{1,2}$ 3.5 Hz, H-1) (Found: C, 60.6; H, 9.6. $C_{16}H_{30}O_6$ requires C, 60.3; H, 9.5%).

Cyclohexyl 2,3,4,6-Tetra-O-methyl-β-D-glucopyranoside (VIII) — Compound (VIII) was prepared from cyclohexyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside[27] (8.0 g) by deacetylation and subsequent methylation as described for the preparation of (VII). The glycoside (VIII) (5.4 g, 91%) was purified by silica gel (Sargent-Welch, 60-200 mesh) chromatography using chloroform-acetone (16:1, vol) as the eluent and subsequent distillation under reduced pressure (0.05 mm Hg) through a 10-cm Vigreux column. The distillate had $[\alpha]_D$ - 27° (c 1.1, $CHCl_3$), δ ($CDCl_3$) 4.34 p.p.m. (1H, d, $J_{1,2}$ 7.0 Hz, H-1) (Found: C, 60.6; H, 9.5. $C_{16}H_{30}O_6$ requires C, 60.3; H, 9.5%).

Cyclohexyl 2-O-Acetyl-3,4,6-tri-O-methyl-α- (IX) and -β-D-glucopyranoside (X) — 3,4,6-Tri-O-methyl-D-glucopyranose[15] (26.4 g) was dissolved in cyclohexanol (130 ml) and acetyl chloride (5 ml). After 3 days of mild heating, t.l.c. (benzene-methanol; 5:1, vol) indicated the glycosidation was complete. The solution was diluted with chloroform (400 ml), washed with water, dried ($CaCl_2$), and concentrated in vacuo to a sirup which was acetylated with acetic anhydride-pyridine[28] (180 ml; 1:2, vol) to yield a mixture of (IX) and (X) (33.3 g, 81%). The anomeric glucosides were separated by silica gel (Sargent-Welch, 60-200 mesh) chromatography using chloroform-ethyl acetate (20:1, vol) as the eluent.

The fractions containing pure α-anomer (IX), as determined by g.l.c. conditions B , were combined, concentrated in vacuo, and distilled under reduced pressure (0.05 mm Hg). The distillate had $[\alpha]_D$ +162° (c 1.0, $CHCl_3$); δ ($CDCl_3$) 5.13 (1H, d, $J_{1,2}$ 3.8 Hz, H-1), 4.64 (1H, m, $J_{2,3}$ ca. 9 Hz, H-2), and 2.08 p.p.m. (3H, s, OAc) (Found: C, 59.0; H, 8.9. $C_{17}H_{30}O_7$ requires C, 58.9; H, 8.7%).

The fractions containing pure β-anomer (X) were combined, concentrated in vacuo, and crystallized from petroleum ether (b.p. 30-60°C) to yield (X); m.p. 58-59°C; $[\alpha]_D$ -25° (c 0.9, $CDCl_3$); δ ($CDCl_3$) 4.40 (1H, d, $J_{1,2}$ ca. 8 Hz, H-1) and 2.08 p.p.m. (3H, s, OAc) (Found: C, 59.1; H, 9.0. $C_{17}H_{30}O_7$ requires C, 58.9; H, 8.7%).

n-Butyl 2,3,4,6-Tetra-O-methyl-β-D-glucopyranoside (XI) — n-Butyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside[27] (57.4) was methylated with dimethyl sulfate as described for the preparation of methyl 2,3,4,6-tetra-O-methyl-β-D-glucopyranoside[23] to yield (XI) as a sirup (32.2 g, 78%) which was purified by distillation under reduced pressure (0.05 mm Hg). The distillate had $[\alpha]_D$ -29° (c 1.0, $CHCl_3$) (Found: C, 57.2; H, 9.5. $C_{14}H_{28}O_6$ requires C, 57.5; H, 9.6%).

Solvents and Reagents – Cyclohexanol[24], chloroform[29], nitromethane[30], benzene[30], and toluene[30] were purified according to published procedures. The silver, mercury, and cadmium compounds were dried in vacuo at 100°C for 24 h and stored in a vacuum desiccator (Drierite).

Reaction Procedures – All glassware was dried at 100°C for 24 h prior to use. The reactions were conducted in a constant temperature room (23°C) in tightly sealed, 100-ml, round bottom flasks wrapped with aluminum foil to eliminate the possible influence of light on the reaction. The reagents, solvents, and glassware were thermally equilibrated in the room overnight before use. The reaction mixtures were stirred (magnetically) continuously to prevent the promoters from settling out.

Cyclohexanol was weighed into a 10-ml volumetric flask, diluted to volume with solvent, and transferred to the reaction flask. The volumetric flask was again filled to volume with solvent which was subsequently transferred to the reaction flask. The internal standard (XI) was weighed into a second 10-ml volumetric flask, diluted to volume with solvent, and transferred to the reaction flask. The volumetric flask was again filled to volume with solvent which was then transferred to the reaction flask. The promoters and powdered Drierite were weighed and transferred to the reaction flask. The system was stirred for one hour prior to addition of the glucosyl bromide. The glucosyl bromide was weighed into a 5-ml volumetric flask, diluted to volume with solvent, and transferred to the reaction flask. The volumetric flask was rinsed with 5.0 ml. of solvent which was transferred to the reaction flask. Finally, iodine, if used, was transferred to the reaction flask.

T.l.c. (isopropyl ether) was used to determine if the reaction was complete. Samples from the 2-O-acetyl-glucosyl bromide (I) reactions were analyzed directly. Samples of the 2-O-methyl-glucosyl bromide (II) reactions were treated with silver nitrate (3%) in acetone-water (19:1, vol) to convert (II) to 2,3,4,6-tetra-O-methyl-D-glucose prior to analysis.

Quantitative Analysis — When complete, the solutions were filtered (Celite) and the residue was rinsed with chloroform. The filtrates were washed as follows: Ag_2O-I_2 reactions, 5% $Na_2S_2O_3$ and water; HgO-$HgBr_2$ reactions, 20% KI and water; $CdCO_3$ and $Hg(CN)_2$ reactions, $NaHCO_3$ and water. Each aqueous phase was back-extracted with chloroform. The combined chloroform extracts were dried ($CaCl_2$) and concentrated *in vacuo*.

Each sample was treated with pyridine-propanoic anhydride (*ca.* 1.5 ml; 1:2, vol) at room temperature with occasional swirling for 24 hours. Water (15 ml) was added to the solution and, after 15 min, the solution was extracted with chloroform (3 x 15 ml). The extracts were washed 1N H_2SO_4 (10 ml), saturated $NaHCO_3$ (10 ml), and water (10 ml). In each case the aqueous phase was back-extracted with a comparable volume of chloroform. The chloroform solutions were then combined for the subsequent wash.

The final chloroform solution was concentrated *in vacuo* and the residue was dissolved in chloroform (1-2 ml) for g.l.c. analysis. Conditions A were employed to analyze the reactions of the 2-*O*-methyl-glucosyl bromide (II); conditions B for reactions of the 2-*O*-acetyl-glucosyl bromide (I).

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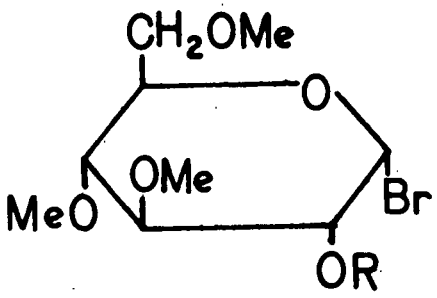
Glycoside analyses for 3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide (ca. 6.5×10^{-2} M) reactions with cyclohexanol at 23°C

Promoter[a]	ROH:RBr:Promoter, mole ratio	Glucosyl Bromide 2-OAc (I) n_β[b]	2-OAc (I) Glucosides, %	2-OMe (II) n_β[b]	2-OMe (II) Glucosides, %
Ag_2O[c]	3:1:1	0.98	85	0.91	95
HgO[d]	3:1:1	0.96	84	0.81	91
$CdCO_3$[e]	3:1:1	0.98	98	0.53	100
$Hg(CN)_2$[f]	3:1:1	0.95	91	0.71	100
$Hg(CN)_2$[f]	10:1:1	0.95	98	0.81	100
$Hg(CN)_2$[f]	30:1:1	0.96	99	0.88	100

[a]Powdered Drierite was employed as a desiccant in each reaction. [b]Mole fraction of β-anomer in the glucosidic products. [c]Iodine (ca. 1.2×10^{-2} M) was employed as a co-catalyst; solvent, chloroform. [d]Mercuric bromide (ca. 3.0×10^{-3} M) was employed as a co-catalyst; solvent, chloroform. [e]Solvent, toluene. [f]Solvent, benzene-nitromethane (1:1, vol).



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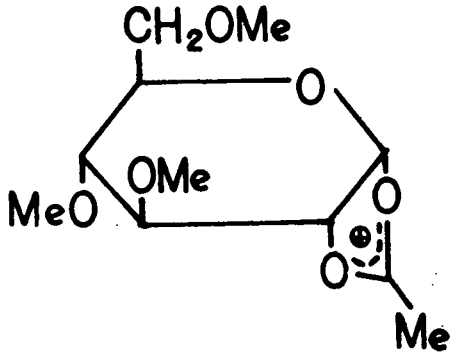
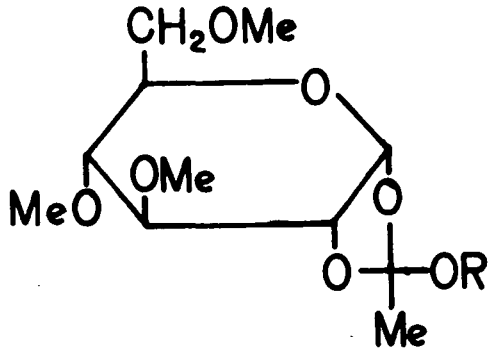
II: R = Me



III



IV: R = Et

V: R = i-Pr

VI: R = Cyclohexyl

Cut 1. Wallace

Koenigs-Knorr Reactions. Part II.[1] A Mechanistic Study of Mercuric Cyanide-Promoted Reactions of 2,3,4,6-Tetra-O-Methyl-α-D-glucopyranosyl Bromide with Cyclohexanol in Benzene-Nitromethane

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ABSTRACT

The kinetics and products of mercuric cyanide-promoted reactions of 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide with cyclohexanol in benzene-nitromethane (1:1, vol) at 2-20°C were investigated by polarimetry and quantitative g.l.c. The reactions exhibited a first-order kinetic dependence on the glucosyl bromide and $Hg(CN)_2$ concentrations, but the reaction rates were independent of the cyclohexanol concentration. Under the conditions employed, cyclohexyl 2,3,4,6-tetra-O-methyl-β-D-glucopyranoside was the main product (ca. 60-80%), but in all reactions the α-glucoside was also formed. The stereoselectivity of the reactions for β-glucoside formation increased when the alcohol concentration was increased and decreased when the reaction temperature was increased. The initial reaction is believed to involve rate-determining, $Hg(CN)_2$-assisted heterolysis of the carbon-bromine bond of the glucosyl bromide to form the glucopyranosyl carboxonium ion. The stereochemical course of the reaction is dependent on the rate of dissociation of the carbonium ion and the attendant anion relative to the rate of reaction of the alcohol with the carbonium ion. Reasons for the observed autocatalysis in the reaction are discussed.

INTRODUCTION

The steric course of Koenigs-Knorr reactions involving 1,2-*cis*-glucopyranosyl halides having a "nonparticipating" C-2 substituent, such as 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide (TMGB), has been found to be extremely variable, ranging from predominantly inversion of configuration at C-1 to predominantly retention of configuration[2-4]. Previously, the steric course of the reaction of TMGB with cyclohexanol was shown to be dependent on both the alcohol concentration and the promoter-solvent system employed[1]. The purpose of this investigation was to determine the mechanism of a reaction of TMGB employing one of the common promoters.

Mechanistic studies of Koenigs-Knorr reactions have been limited primarily to studies of alcoholyses not involving the use of promoters or acid acceptors[5-7], with some notable exceptions[8]. This is probably due to the fact that the heterogeneous nature of reactions employing insoluble promoters makes it difficult to obtain reliable kinetic data. In this paper the results of a study of reactions of TMGB with cyclohexanol in the presence of mercuric cyanide in benzene-nitromethane (1:1, vol)[9] are reported. The solubility of mercuric cyanide in the reaction solvent permitted the use of both kinetic measurements and product analyses in the study of the reaction mechanism.

RESULTS

Initial rates for the mercuric cyanide-promoted reactions of TMGB with cyclohexanol were calculated from the initial linear portion of plots of the glucosyl bromide concentration *versus* time. The concentration of TMGB as a function of time was determined from polarimetric data and Equation (1)[10].

$$[TMGB] = [TMGB]_o \, (\alpha_t - \alpha_\infty) \, (\alpha_o - \alpha_\infty)^{-1} \qquad (1)$$

where $[TMGB]_o$ = the initial TMGB concentration, α_t = the optical rotation of the reaction system at time t, $\alpha_o = \alpha_t$ at time zero (determined by extrapolation), and $\alpha_\infty = \alpha_t$ at long reaction time (equilibrium rotation). Equation (1) is valid only if the ratio of anomers in the glucosidic products is time-independent. Anomeric glucopyranoside analyses as a function of time for reactions employing various ratios of reactant concentrations and reaction temperatures, reported for selected reactions in Table 1, demonstrated that this requirement was fulfilled by the reactions of TMGB.

A graphical determination of the initial rate for a reaction of TMGB is shown in Figure 1. The deviation from linearity is believed to have been due to the catalyzing effect of species formed by the reaction. The initial reaction rate, $(d[TMGB]/dt)_{t=0}$, was determined (method of least squares) from the initial linear portion of the curve.

The order of the reaction with respect to each reactant was calculated from initial reaction rates for series of reactions at 10°C, in which the concentration of only one reactant was varied at a time. Plots of log $(d[TMGB]/dt)_{t=0}$ *versus* log $[TMGB]_{t=0}$, log $[Hg(CN)_2]_{t=0}$, and log $[ROH]_{t=0}$ are shown in Figure 2. Experimentally, the order of reaction with respect to both TMGB and $Hg(CN)_2$ was *ca.* 1.00. The reaction rate was independent of the cyclohexanol (ROH) concentration. Therefore, the initial rate of the reaction is described by Equation (2).

$$(d[TMGB]/dt)_{t=0} = -k[TMGB] \, [Hg(CN)_2] \qquad (2)$$

The initial rate constants, k, required for calculation of the thermodynamic functions of activation, were determined from the initial rates of reaction and Equation (2). Initial rate constants for various temperatures, and the enthalpy ($\Delta H^{\ddagger}$) and entropy ($\Delta S^{\ddagger}$) of activation for mercuric cyanide-promoted reactions of TMGB are given in Table 2.

The effects of variations in the cyclohexanol, TMGB, and $Hg(CN)_2$ concentrations, and the reaction temperature on the anomeric composition of the glucosidic products is shown in Table 1. Increasing the alcohol concentration or decreasing the reaction temperature resulted in an increase in the selectivity of the reaction for formation of the β-glucoside. Variation of the $Hg(CN)_2$ and TMGB concentrations had no apparent effect on the stereoselectivity of the reaction.

DISCUSSION

The fact that the reaction of TMGB exhibits first-order kinetic dependence on both the TMGB and $Hg(CN)_2$ concentrations, but is independent of the cyclohexanol concentration indicates that the reaction occurs by a mechanism in which heterolysis of the carbon-bromine bond is assisted by the $Hg(CN)_2$ in the rate-determining step of the reaction. Analogous enhancement of reactions of glycosyl halides by mercury(II) halides has been demonstrated previously[11]. The rate-limiting step is then followed by a much faster reaction of the resultant glucopyranosyl carboxonium ion with cyclohexanol to form glucosides.

The mechanism by which the $Hg(CN)_2$ assists in heterolysis of the carbon-bromine bond of TMGB is unknown. The $Hg(CN)_2$ may complex reversibly with the glucosyl bromide (RBr). In a unimolecular, rate-determining step the carbonium ion (R^+) would be formed from the complex as depicted in Equation (3). Alternatively, the $Hg(CN)_2$ may assist in bond cleavage through its reaction with the glucosyl bromide in a bimolecular rate-limiting step as depicted in Equation (4). The existence of ions of the type HgX_3^-, as proposed in either Equation (3) or Equation (4) is well established[11,12].

$$RBr + Hg(CN)_2 \rightleftharpoons RBr{:}Hg(CN)_2 \overset{\text{slow}}{\rightleftharpoons} R^+ + BrHg(CN)_2^- \qquad (3)$$

$$RBr + Hg(CN)_2 \overset{\text{slow}}{\rightleftharpoons} \underset{\text{Transition State}}{[R^{\delta+}\cdots Br^{\delta-}\cdots Hg(CN)_2]^{\ddagger}} \rightleftharpoons R^+ + BrHg(CN)_2^- \qquad (4)$$

The fact that $Hg(CN)_2$ assists in rate-determining heterolysis of the carbon-bromine bond is also reflected in both the enthalpy and entropy of activation for reaction of TMGB (Table 2). Such assistance would decrease the energy required for bond cleavage and this is reflected in the relatively low value for $\Delta H^{\ddagger}$ (10 kcal mol^{-1}). The loss of freedom associated with $Hg(CN)_2$ being coordinated with TMGB in the transition state of the rate-determining step of the reaction is reflected in both the sign and magnitude of $\Delta S^{\ddagger}$ (-29 e.u.). Similar enthalpy and entropy of activation values have been reported for mercuric chloride-catalyzed methanolysis of tetra-O-acetyl-α-D-gluco-pyranosyl chloride[11].

The observed influence of the alcohol concentration on the configuration of the glucosidic products (Table 1) indicates that the carbonium ion resulting from heterolysis of the carbon-bromine bond is partially shielded by the departing anion, or that these ions exist for a time as an ion pair. Reaction of the alcohol with the shielded carbonium ion would result in formation of the β-glucoside. However, when dissociation of the ions is complete, the alcohol can react at either the α- or β-side of the carbonium ion resulting in formation of both the α- and β-glucoside. As the alcohol concentration is increased, the availability of the alcohol to react with the carbonium ion increases. Thus, the rate of reaction of the alcohol with the shielded carbonium ion or ion pair increases relative to the rate of dissociation of the ions. Therefore, an increase in the alcohol concentration leads to an increase in the ratio of β-glucoside formed (Table 1).

As mentioned, formation of the α-glucoside is believed to be due to reaction of the alcohol with the free or unshielded carbonium ion. Alternatively, halide exchange (α-ion pair $\underset{}{\overset{Br^-}{\rightleftharpoons}}$ β-ion pair)[2,4,13] could potentially account for the observed partial retention of configuration at C-1. However, the latter

explanation is inconsistent with the fact that the ratio of anomeric glucosides was found to be time-independent (Table 1).[14]

The dependence of the glucosidic product configuration on the reaction temperature (Table 1) indicates that an increase in the reaction temperature results in an increase in the relative importance of glucoside formation via the free or unshielded carbonium ion. An increase in the reaction temperature must increase the rate of dissociation of the ions to a greater degree than the rate of reaction of the alcohol with the shielded carbonium ion, and thereby increase the relative amount of α-glucoside formed.

The reaction scheme shown in Figure 3 represents what is believed to be the initial mechanism for glucoside formation in the mercuric cyanide-promoted reaction of TMGB with cyclohexanol in benzene-nitromethane (1:1, vol). The rate-determining step, heterolysis of the carbon-bromine bond of TMGB assisted by $Hg(CN)_2$, results in formation of a shielded carbonium ion, probably an ion pair. If the alcohol reacts with the carbonium ion before the carbonium ion dissociates from its attendant anion only the β-glucoside is formed; after dissociation of the ions either the α- or β-glucoside can be formed. The rate of dissociation of the ions relative to the rate of reaction of the alcohol with the carbonium ion determines the stereochemical course of the reaction.

Based on the observed autocatalysis for the reaction of TMGB (Figure 1)[10], species must be formed which, in addition to $Hg(CN)_2$, assist in the heterolysis of the carbon-bromine bond. Species potentially capable of functioning as promoters are HgBrCN, $HgBr_2$, HCN, HBr, and H^+ which could presumably be formed by reactions indicated in Equations (5)-(10).

$$RBr + Hg(CN)_2 \rightleftharpoons R^+ + Hg(CN)_2Br^- \quad (5)$$

$$R^+ + R'OH \longrightarrow ROR' + H^+ \quad (6)$$

$$Hg(CN)_2Br^- + H^+ \rightleftharpoons HgBrCN + HCN \quad (7)$$

$$Hg(CN)_2Br^- + H^+ \rightleftharpoons Hg(CN)_2 + HBr \quad (8)$$

$$RBr + HgBrCN \rightleftharpoons R^+ + HgBr_2CN^- \quad (9)$$

$$HgBr_2CN^- + H^+ \rightleftharpoons HgBr_2 + HCN \quad (10)$$

A comparison of the half-lives ($t_{1/2}$) of mercuric cyanide- and mercuric bromide-promoted reactions of TMGB is given in Table 3. The mercuric bromide-promoted reaction had a much lower $t_{1/2}$ (1.4 min) than did the mercuric cyanide-promoted reaction (9.5 min), even though the concentration of $HgBr_2$ was approximately one-half the concentration of $Hg(CN)_2$. Thus, $HgBr_2$ is a more effective promoter for the reaction of TMGB under these conditions than $Hg(CN)_2$. It would be expected that the capability of HgBrCN to facilitate the reaction of TMGB would be between that of $HgBr_2$ and $Hg(CN)_2$. Previous studies have shown that HBr is also an effective catalyst for reactions of glycosyl bromides[11,14]. Presumably HCN and other protic acids would act similar to HBr.

Equation (2), which is the initial rate equation for the TMGB reaction, must therefore be expanded to include the effect of all species capable of facilitating the reaction to arrive at the general rate expression, Equation (11).

$$d[TMGB]/dt = - [TMGB] \sum_{1}^{i} k_i[A_i] \quad (11)$$

where $[A_i]$ = the concentration of catalyst i and k_i = the second-order rate constant corresponding to A_i.

EXPERIMENTAL

Analytical Methods — M.p.s., elemental analyses, and p.m.r. spectra were determined as described previously[1]. T.l.c. was performed on silica gel G utilizing methanolic sulfuric acid (5:1, wt) spray with charring for component detection.

The g.l.c. instrument was described previously[1]. Analyses were performed on a column (3 ft x 0.125 in o.d., stainless steel) of 30% Carbowax 20M on 60-80 mesh Chromosorb W using N_2, 60 ml min^{-1}; column, 160°C for 51 min then 160° → 220°C at 20° min^{-1}; injector, 205°C; and detector, 265°C.

Polarimetric analyses were made on a Perkin-Elmer 141 MC polarimeter. The constant temperature system used for kinetic studies has been described previously[14,15]. The cell used was glass with a glass jacket forming an annulus for circulating water around the cell, was 1 dm long, and held ca. 5 ml of solution.

Solvents and Reagents — Cyclohexanol[14], ethanol[16], and methanol[16] were purified according to published procedures.

Mercuric cyanide (25 g) was dissolved in hot absolute ethanol (200 ml), and a portion of the alcohol was distilled off to azeotropically dry the solution. The $Hg(CN)_2$ which crystallized upon refrigeration of the solution was dried in vacuo at 100°C for 24 h and stored in a vacuum desiccator (P_2O_5).

Thiophenol was dried ($CaCl_2$) and fractionally distilled (40-cm Vigreux column) with the exclusion of moisture. Benzene was subjected to a preliminary drying ($CaCl_2$), refluxed with $LiAlH_4$, and fractionally distilled (40-cm Vigreux column) from $LiAlH_4$ with the exclusion of moisture. Nitromethane was successively percolated through Drierite, fractionally distilled (40-cm Vigreux column),

percolated through Drierite, and fractionally distilled with the exclusion of moisture.

Compound Syntheses — General. 2,3,4,6-Tetra-O-methyl-α-D-glucopyranosyl bromide, n-butyl 2,3,4,6-tetra-O-methyl-β-D-glucopyranoside, cyclohexyl 2,3,4,6-tetra-O-methyl-α-D-glucopyranoside, and cyclohexyl 2,3,4,6-tetra-O-methyl-β-D-glucopyranoside were prepared as described previously[1].

2,3,4,6-Tetra-O-methyl-1-O-propanoyl-D-glucopyranose — 2,3,4,6-Tetra-O-methyl-D-glucopyranose[17] (2.0 g) was treated with propanoic anhydride-pyridine (12 ml; 1:2, vol) for 12 h. The solution was stirred with ice water for 0.5 h and extracted with chloroform (3 x 20 ml). The chloroform extracts were washed with 1N H_2SO_4, saturated $NaHCO_3$, and water; dried ($CaCl_2$); and concentrated *in vacuo* to a sirup which was fractionally distilled under reduced pressure (0.05 mm Hg) through a 10-cm Vigreux column. The distillate had $[\alpha]_D$ + 74° (*c* 1.0, $CHCl_3$) (Found: C, 53.5; H, 8.4. $C_{13}H_{24}O_7$ requires C, 53.4; H, 8.4%).

Phenyl 2,3,4,6-Tetra-O-methyl-1-thio-β-D-glucopyranoside — 2,3,4,6-Tetra-O-methyl-α-D-glucopyranosyl bromide (4.9 g) in chloroform (100 ml) was treated with thiophenol (37.0 g) in 1M methanolic sodium methoxide (170 ml). The reaction, which was monitored by t.l.c. (benzene-ethyl acetate; 1:1, vol), was complete within 1 min. The reaction was diluted with water (100 ml) and extracted with chloroform (3 x 100 ml). The extracts were washed with 10% Na_2CO_3 (3 x 150 ml) and water (150 ml), dried ($CaCl_2$), and concentrated *in vacuo* to a sirup (4.7 g, 87%). Crystallization of the product from petroleum ether (b.p. 60-110°C) yielded phenyl 2,3,4,6-tetra-O-methyl-1-thio-β-D-glucopyranoside; m.p. 70.5-72°C, $[\alpha]_D$ -35.9° (*c* 1.0, $CHCl_3$), δ ($CDCl_3$) 4.50 (1H, d, $J_{1,2}$ 9.2 Hz, H-1) and 7.1-7.7 p.p.m. (5H, m, $-SC_6H_5$) (Found: C, 58.8; H, 7.3; S, 9.9. $C_{16}H_{24}O_5S$ requires C, 58.5; H, 7.3; S, 9.8%).

Reaction Initiation and Polarimetric Analysis — Anhydrous conditions were imperative throughout the procedures given below because of the sensitivity of the glucosyl bromide to hydrolysis. All glassware was dried at 180°C for 24 h and stored in a vacuum desiccator (P_2O_5). Solvent transfers and weighing of compounds were conducted in a dry atmosphere to reduce the possibility of contamination by water.

Mercuric cyanide was weighed into a 50-ml volumetric flask. Anhydrous nitromethane (35 ml) was pipetted into the volumetric flask, and the mercuric cyanide was dissolved by refluxing the nitromethane. Subsequently, nitromethane (10 ml) was distilled from the flask to azeotropically dry the system. The flask was allowed to cool and weighed to determine the amount of nitromethane employed in the reaction. Cyclohexanol was then weighed into the volumetric flask.

Anhydrous benzene (35 ml) was pipetted into a second 50-ml volumetric flask. Benzene (10 ml) was distilled from the flask to azeotropically dry the system. The flask was allowed to cool and weighed to determine the amount of benzene employed in the reaction. 2,3,4,6-Tetra-O-methyl-α-D-glucopyranosyl bromide was then weighed into the flask.

The two volumetric flasks were allowed to thermally equilibrate in a bath at the desired reaction temperature for 30 min. A bent (45°) connecting tube was placed between the flasks and the contents of the two flasks were mixed together. Time zero for the reaction was taken to be the point at which mixing was begun. A sampling chamber[17] was attached to the flask containing the reaction solution to reduce the possibility of contamination by water during sampling, and the flask was returned to the constant temperature bath.

A sample of the reaction solution was immediately transferred to a polarimeter cell at the desired reaction temperature. Readings were begun approximately one minute from the time the reaction was initiated.

Quantitative G.l.c. Analysis — The reactant and carbohydrate products of the TMGB reactions were identified and measured quantitatively by g.l.c. Prior to g.l.c. analysis, samples of the reactions were subjected to a series of chemical reactions in which unreacted TMGB was converted to phenyl 2,3,4,6-tetra-O-methyl-1-thio-β-D-glucopyranoside and 2,3,4,6-tetra-O-methyl-D-glucopyranose, the product of any hydrolysis of TMGB which might have occurred, was converted to 2,3,4,6-tetra-O-methyl-1-O-propanoyl-D-glucopyranose.

Aliquots (5 ml) of the reaction, taken to determine the ratio of anomeric glucosides as a function of time, were pipetted into a solution (0.66 ml) of thiophenol in 0.5M methanolic sodium methoxide (1:10, vol). The desired amount of a standard solution (ca. 0.05M) of internal standard, n-butyl 2,3,4,6-tetra-O-methyl-β-D-glucopyranoside, in chloroform was added to the samples which were then concentrated in vacuo to an oil. The oil was treated with propanoic anhydride-pyridine (ca. 2 ml; 1:2, vol) at room temperature with occasional swirling for 24 h. Water (15 ml) was added and, after 15 min, the mixture was extracted with chloroform (3 x 15 ml). The chloroform extracts were washed with 2N HCl in saturated NaCl (10 ml), 1N NaOH in 10% NaCl (10 ml), and water (10 ml). After each washing the aqueous phase was back-extracted with a comparable volume of chloroform. The chloroform solutions were then combined for the succeeding stage of the procedure. The resultant chloroform solution was concentrated in vacuo to an oil. In cases where residual propanoic acid was noted, it was removed as its aqueous azeotrope by adding several ml of water and reconcentrating. The oil was dissolved in chloroform (ca. 0.5 ml) and analyzed by g.l.c.

The response factors required for quantitative g.l.c. were determined by subjecting synthetic mixtures of the necessary compounds to the analysis procedure.

The g.l.c. retention times (min) were: n-butyl 2,3,4,6-tetra-O-methyl-β-D-glucopyranoside (12.3), 2,3,4,6-tetra-O-methyl-1-O-propanoyl-D-glucopyranose (anomers, 23.0 and 28.4), cyclohexyl 2,3,4,6-tetra-O-methyl-β-D-glucopyranoside (38.4), cyclohexyl 2,3,4,6-tetra-O-methyl-α-D-glucopyranoside (42.8), and phenyl 2,3,4,6-tetra-O-methyl-1-thio-β-D-glucopyranoside (68.7).

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Table 1

Anomeric Glucopyranoside Analyses

Variable	ROH:TMGB:$Hg(CN)_2$, Mole Ratio[a]	Temp., (°C)	Reaction[b], (%)	n_α[c]
Cyclohexanol	7.5:1:1	10	12	0.28
			33	0.27
			100	0.29
	15:1:1	10	13	0.24
			29	0.23
			100	0.23
	22.5:1:1	10	100	0.18
TMGB	15:0.5:1[d]	10	7	0.25
			17	0.23
			100	0.24
	15:1:1	10	100	0.23
$Hg(CN)_2$	15:1:0.5	10	5	0.26
			14	0.24
			100	0.24
	15:1:1	10	100	0.23
	15:1:1.5	10	100	0.23
	15:1:2	10	100	0.21
Temperature	15:1:1	2	100	0.17
	15:1:1	5	100	0.18
	15:1:1	10	100	0.23
	15:1:1	15	100	0.23
	15:1:1	20	17	0.24
			26	0.25
			100	0.26

[a] TMGB, ca. 6×10^{-3} M.
[b] Determined from polarimetric data.
[c] Mole fraction of α-anomer in the glucosidic products. Analyses of standards indicated that n_α could be determined within ± 2 mol percent.
[d] TMGB, ca. 3×10^{-3} M.

Table 2

Initial Rate Constants and Thermodynamic Functions of Activation

Temp. (°C)	$10^2 k$ (l mole^{-1} sec^{-1})[a]	$\Delta H^{\ddagger}$ (kcal mole^{-1})	$\Delta S^{\ddagger}$ (e.u.)[b]
20	8.72	10.0	-29.1
15	6.06		
10	4.67		
5	3.45		
2	2.36		

[a] Average of duplicate determinations.
[b] Calculated for 20°C.

Table 3

Half-lives for Mercuric Cyanide- and Mercuric Bromide- Facilitated Reactions of 2,3,4,6-Tetra-O-Methyl-α-D-glucopyranosyl Bromide with Cyclohexanol (10°C)[a]

TMGB (10^3M)	Cyclohexanol (10^2M)	$Hg(CN)_2$ (10^3M)	$HgBr_2$ (10^3M)	$t_{1/2}$[b] (min)
5.862	9.024	5.984	--	9.5
2.948	4.508	--	2.993	1.4

[a] Benzene-nitromethane (1:1, vol) solvent.

[b] Time necessary for one-half of the glucosyl bromide to react. The half-life of each reaction is a function of the concentration of reactants, particularly the mercuric cyanide and mercuric bromide concentrations.

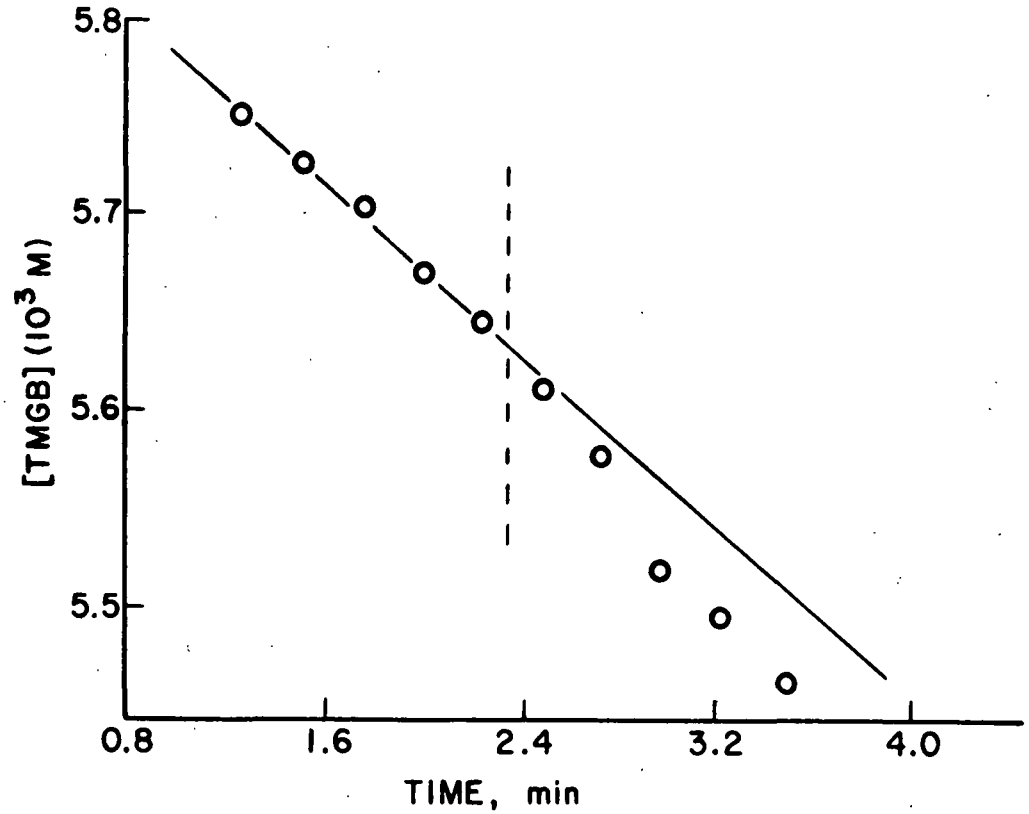

Fig. 1. Initial reaction rate determination: 10°C; TMGB, 5.86×10^{-3} M; $Hg(CN)_2$, 5.98×10^{-3} M. Initial slope = $(d[TMGB]/dt)_{t=0} = -1.75 \times 10^{-6}$ mol l^{-1} sec^{-1}

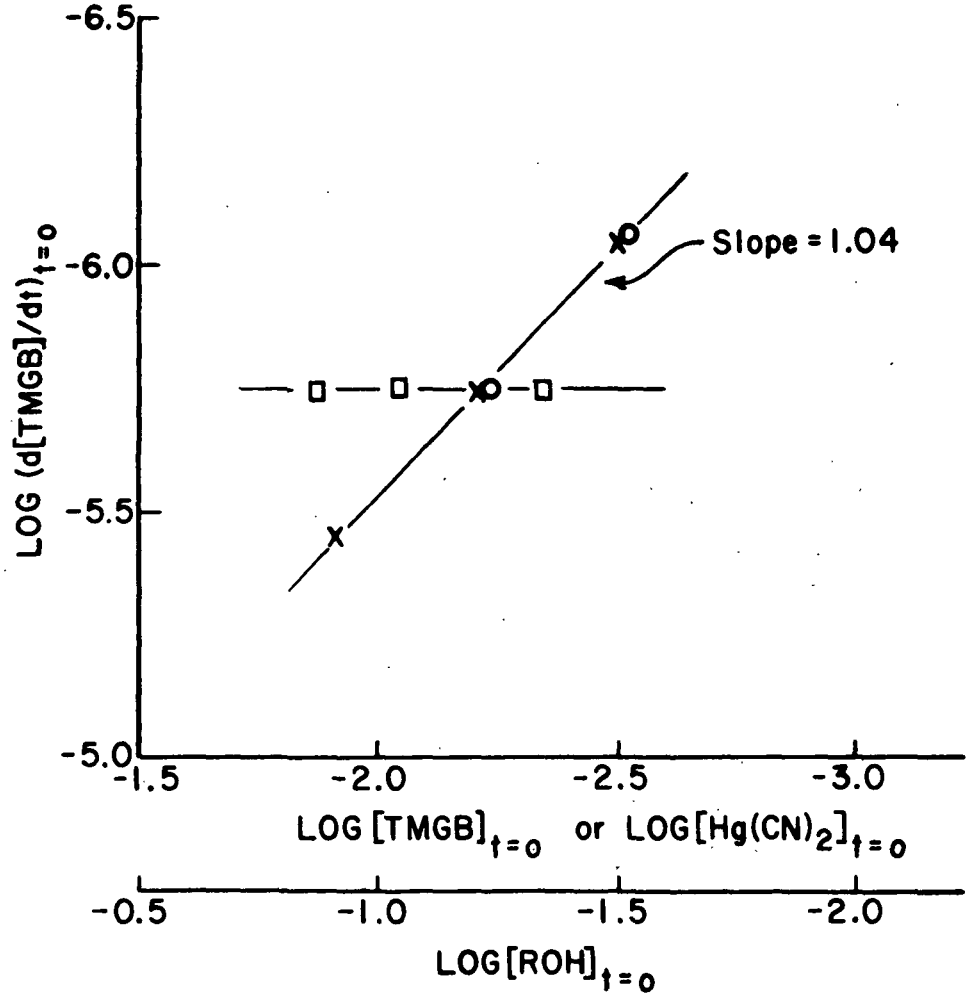

Fig. 2. Reaction order determinations at 10°C. O — TMGB; X — $Hg(CN)_2$; □ — cyclohexanol (ROH)

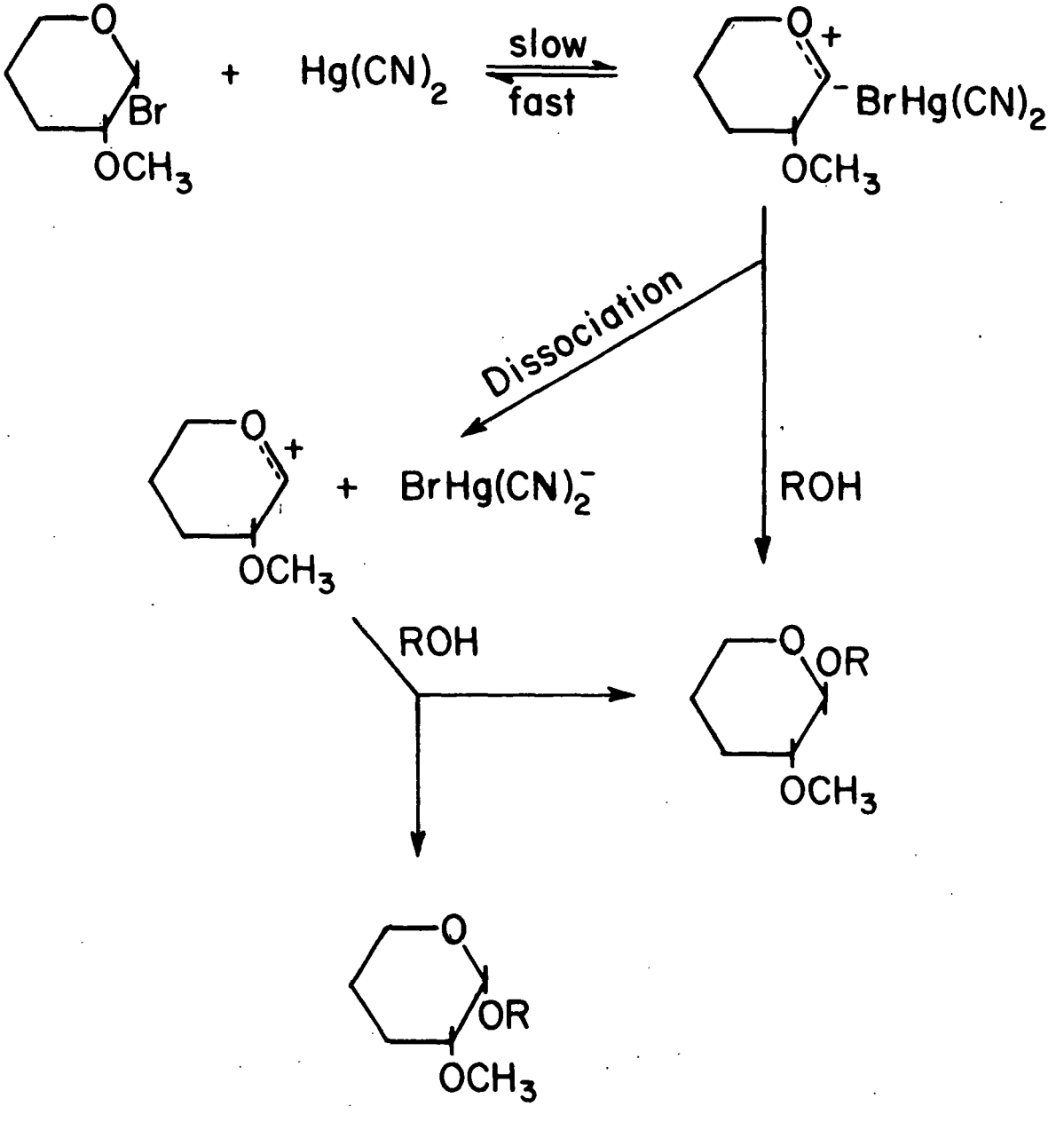

Fig. 3. Proposed mechanism for glucoside formation in mercuric cyanide-promoted reactions of 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide with cyclohexanol in benzene-nitromethane (3,4, and 5 substituents of the pyranoid rings are not shown)

Koenigs-Knorr Reactions. Part III.[1] A Mechanistic Study of Mercuric Cyanide-Promoted Reactions of 2-O-Acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl Bromide with Cyclohexanol in Benzene-Nitromethane

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ABSTRACT

The kinetics and products of reactions of 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide (I) with cyclohexanol in the presence of $Hg(CN)_2$ in nitromethane-benzene (1:1, vol) at 10-25°C were investigated by polarimetry, g.l.c., and p.m.r. The reactions exhibited a first-order kinetic dependence on the glucosyl bromide and $Hg(CN)_2$ concentrations, but the reaction rates were independent of the cyclohexanol concentration. Cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucopyranoside (IV) was the major final product (>90%) in reactions. The initial reaction is believed to involve rate-determining, $Hg(CN)_2$-assisted heterolysis of the carbon-bromine bond to form the glucopyranosyl carboxonium ion. Glucoside formation then results from reaction of the alcohol with the carboxonium ion as the ion pair, the dissociated carboxonium ion, or an intermediate orthoester, 1,2-O-(1-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose (III). The orthoester (III) was shown to selectively form the β-glucoside (IV) under the reaction conditions used. The mole fraction of orthoester (III) in the initial reaction products was always substantially greater than that of cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranoside (V) and increased as the alcohol concentration decreased. Stereoselective formation of the β-glucoside (IV) in the overall reaction of the glucosyl bromide (I) is due to the fact that in those reactions of (I) which do not yield (IV) directly, α-glucoside (V) formation is minimized by preferential formation of the orthoester (III) which selectively forms the β-glucoside (IV).

INTRODUCTION

The steric course of Koenigs-Knorr reactions involving 1,2-*cis*-glycosyl halides has been found to be greatly influenced by the nature of the C-2 substituent. Reactions of 1,2-*cis*-glycosyl halides having a 2-*O*-acyl substituent generally proceed with a high degree of inversion of configuration at C-1[2-4], whereas the steric nature of the glycosidic products of the reactions of 1,2-*cis*-glycosyl halides having a "nonparticipating" C-2 substituent is extremely variable[5-7]. In a previous study[8], it was found that reactions of 2-*O*-acetyl-3,4,6-tri-*O*-methyl-α-D-glucopyranosyl bromide (I) with cyclohexanol utilizing various promoters and alcohol concentrations selectively formed the 1,2-*trans*-glucoside. In contrast, similar reactions of 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranosyl bromide were less selective, and the selectivity was very dependent on the alcohol concentration and on the promoter employed.

It has been postulated[4] that the stereoselectivity of *cis*-2-*O*-acetyl-glycosyl halide (e.g., I) reactions arises because the acetoxy group at C-2 participates in the reaction by formation of the cyclic 1,2-acetoxonium ion (e.g., II) which directs the incoming nucleophile into the 1,2-*trans* position. However, reaction of an alcohol with the 1,2-acetoxonium ion should result in preferential formation of an orthoester (e.g., III) rather than the glycoside[9,10]. In a subsequent reaction, provided that the reaction conditions are suitable, the orthoester can selectively form 1,2-*trans*-glycosides.[10,11] Orthoesters have been reported as products in Koenigs-Knorr reactions of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide employing silver salts as promoters[12,13], but it has not, to our knowledge, been demonstrated that orthoesters can act as important intermediates for glycoside formation in a Koenigs-Knorr reaction employing one of the typical promoters.

In this paper we report the results of a detailed study of the mercuric cyanide-promoted reaction of 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide (I) with cyclohexanol in benzene-nitromethane (1:1, vol). The mechanism of the reaction, particularly the potential contribution of an orthoester (III) intermediate to the stereochemistry of the reaction, was of interest.

[Cut 1 here]

RESULTS AND DISCUSSION

Orthoester Formation — The average mole fraction of initial reactant accounted for by quantitative g.l.c. analyses of the carbohydrates as a function of time was 1.02 ($\sigma \pm 0.03$).

As illustrated in Figure 1, the initial products of the mercuric cyanide-promoted reaction of the glucosyl bromide (I, RBr) with cyclohexanol (ROH) in benzene-nitromethane (1:1, vol) were primarily cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucopyranoside (IV), cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranoside (V), and 1,2-O-(1-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose (III). The concentration of the orthoester (III) increased as the glycosyl bromide (I) reacted, but when (I) was essentially depleted, the concentration of (III) decreased with a concurrent increase in the concentration of the β-glucoside (IV). Thus, part of the major reaction product, the 2-O-acetyl-β-glucoside (IV), was formed from the orthoester (III). The normalized mole fractions* of glucosidic products after the orthoester (III)

*The mole fractions of glucosidic products are reported on a normalized basis because some hydrolysis products were always formed despite the extreme care taken to eliminate traces of water from the reaction systems. In this reaction approximately 5% of the initial reactants was accounted for as hydrolysis products. The hydrolysis products are believed to originate primarily from the orthoester (III) which will hydrolyze readily and in preference to forming glycosides[9].

had reacted completely were: cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucopyranoside (IV), 0.92; cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranoside (V), 0.06; cyclohexyl 3,4,6-tri-O-methyl-β-D-glucopyranoside (VI), 0.01; and cyclohexyl 3,4,6-tri-O-methyl-α-D-glucopyranoside (VII), 0.01.

[Fig. 1 here]

The data in Figure 1 were obtained by a procedure in which the orthoester (III), unstable to direct g.l.c. analysis, was analyzed as its hydrolysis products*, 1-O-acetyl- (VIII) and 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranose (IX)[9]. To obtain supporting evidence for formation of orthoesters in mercuric cyanide-promoted reactions of the glucosyl bromide (I) with alcohols, the reactant and intermediate products of (I) with ethanol were isolated *in toto* and analyzed by p.m.r. (Figure 2). Ethanol was substituted for cyclohexanol because the broad multiplet from cyclohexyl ring protons masks the characteristic singlet of the dioxolane 2-methyl group of a 1,2-(alkyl orthoacetate) of D-glucopyranose. The singlet at δ 1.67 p.p.m. ($CDCl_3$) in Figure 2 is indicative of the dioxolane 2-methyl group of 1,2-O-(1-*exo*-ethoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose (X)[9]. Addition of known (X) to the sample increased the amplitude of the singlet while shaking the sample with acidic D_2O rapidly eliminated the singlet.

[Fig. 2 here]

To determine the amount of orthoester (III) formed in a mercuric cyanide-promoted reaction of (I) with cyclohexanol, mercuric oxide was added to the system to neutralize protic acids produced and thereby decrease the

*The analytical procedure permitted differentiation between hydrolysis products formed during the reaction and those formed from the orthoester during analysis.

rate of conversion of the orthoester (III) to glycosides. Reactant and product mole fractions as a function of time are shown in Figure 3. In contrast to the unbuffered reaction (Figure 1), the mole fraction of orthoester (III) remained constant after the glucosyl bromide (I) was depleted. In addition, the orthoester (III) constituted ca. 45% of the reaction products, thus indicating its importance as an intermediate in glycoside formation in the reaction of the glucosyl bromide (I) under these conditions.

[Fig. 3 here]

The reaction of the orthoester (III) with cyclohexanol in benzene-nitromethane was also studied independently. Both $Hg(CN)_2$ and HBr were added to the system as catalysts. The reaction of (III) using only $Hg(CN)_2$ as a catalyst was extremely slow[14]. Therefore, HBr, which is formed when the glucosyl bromide (I) reacts with an alcohol, was used as a cocatalyst. A reaction of the orthoester (III) (ca. 5.0×10^{-3} M) at 10°C and an initial reactant mole ratio of 1:1:1:15 (orthoester (III):$Hg(CN)_2$:HBr:cyclohexanol) had a half-life of approximately 35 min. The normalized mole fractions of glucosidic products were: cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucopyranoside (IV), 0.89; cyclohexyl 3,4,6-tri-O-methyl-β-D-glucopyranoside (VI), 0.06; and cyclohexyl 3,4,6-tri-O-methyl-α-D-glucopyranoside, 0.05. The product distribution further demonstrates that under the conditions of the glucosyl bromide (I) reactions, the orthoester (III) selectively forms the 2-O-acetyl-β-D-glucoside (IV).

Kinetic Analysis — The initial rates of the glucosyl bromide (I) reactions, $(d[RBr]/dt)_{t=0}$, were determined (method of least squares) from the initial linear portions of plots of the concentration of the glucosyl bromide versus time, e.g. Figure 4. The concentration of the glucosyl bromide (I) was

determined from polarimetric data and Equation (1)[14,15].

$$[RBr] = [RBr]_o \ (\alpha_t - M)(\alpha_o - M)^{-1} \qquad (1)$$

where [RBr] = the concentration of (I) at time $\underline{t}$; $[RBr]_o$ = the initial concentration of (I); $\alpha_{\underline{t}}$ = the optical rotation of the reaction system at time $\underline{t}$; $\alpha_o = \alpha_{\underline{t}}$ at time zero (determined by extrapolation); $\underline{M} = \underline{l}(\underline{n_a}[\alpha_{\underline{a}}] + \underline{n_b}[\alpha_{\underline{b}}] + \underline{n_c}[\alpha_{\underline{c}}])\underline{M_G}[RBr]_o/1000$; $\underline{l}$ = the polarimeter cell length (dm); $\underline{M_G}$ = the gram-molecular weight of the anomeric glucosides, (IV) and (V), and the orthoester (III); $\underline{n_a}$, $\underline{n_b}$, and $\underline{n_c}$ = the mole fractions of the initial products accounted for by (V), (IV), and (III), respectively; and $[\alpha_{\underline{a}}]$, $[\alpha_{\underline{b}}]$, and $[\alpha_{\underline{c}}]$ = the specific optical rotations of (V), (IV), and (III), respectively, in the reaction system. The values of $\underline{n_a}$, $\underline{n_b}$, and $\underline{n_c}$ were obtained by extrapolating the product mole ratios determined by g.l.c. analyses to zero time. The specific optical rotations of (III), (IV), and (V) were determined as a function of temperature in benzene-nitromethane (1:1, vol)[14].

[Fig. 4 here]

The reactions exhibited autocatalysis (e.g. Figure 3). As discussed previously[1], some potential catalysts which may be formed in a mercuric cyanide-promoted reaction of a glycosyl bromide are HgBrCn, $HgBr_2$, HCN, HBr, and H^+. It was demonstrated that $HgBr_2$ is a more effective catalyst for the reaction of (I) under these conditions than $Hg(CN)_2$[14].

The order of the reaction with respect to each reactant was calculated from initial reaction rates for series of reactions at 10°C, in which the concentration of only one reactant was varied at a time. Plots of $\log (d[RBr]/dt)_{t=0}$ *versus* $\log[RBr]_{t=0}$, $\log[Hg(CN)_2]_{t=0}$, and $\log[ROH]_{t=0}$ are shown in Figure 5. Experimentally, the order of reaction with respect to both the glucosyl bromide (I) and $Hg(CN)_2$ was *ca.* 1.00. The reaction rate was independent of the cyclohexanol

(ROH) concentration. Therefore, the initial rate of the reaction is described by Equation (2), analogous to the rate expression determined for mercuric

$$(d[RBr]/dt)_{t=0} = -k[RBr][Hg(CN)_2] \qquad (2)$$

cyanide-promoted reactions of 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide (XI)[1].

[Fig. 5 here]

The fact that the initial reactions of the glucosyl bromide (I) exhibit first-order kinetic dependence on both the bludosyl bromide (I) and $Hg(CN)_2$ concentrations, but are independent of the cyclohexanol concentration indicates, as with analogous reactions of (XI)[1], that the reactions occur by a mechanism in which heterolysis of the carbon-bromine bond is assisted by the $Hg(CN)_2$ in the rate-determining step of the reaction. In a subsequent fast reaction the resultant glucopyranosyl carboxonium ion forms either glucosides, (IV) or (V), or the orthoester (III). The mechanism by which the $Hg(CN)_2$ assists in heterolysis of the carbon-bromine bond of (I) is unknown. However, at least two mechanisms can be envisioned for the reaction. The $Hg(CN)_2$ may complex reversibly with the glucosyl bromide. In a unimolecular, rate-determining step the carbonium ion (R^+) would be formed from the complex (Equation 3). Alternatively, the $Hg(CN)_2$ may assist in bond cleavage through a bimolecular rate-limiting step [Equation (4)]. The existence of ions of the type HgX_3^-, as proposed for either mechanism is well established[16,17].

$$RBr + Hg(CN)_2 \rightleftharpoons RBr{:}Hg(CN)_2 \overset{\text{slow}}{\rightleftharpoons} R^+ + BrHg(CN)_2^- \qquad (3)$$

$$RBr + Hg(CN)_2 \overset{\text{slow}}{\rightleftharpoons} \underset{\text{Transition State}}{[R^{\delta+}\text{----}Br^{\delta-}\text{----}Hg(CN)_2]^{\ddagger}} \rightleftharpoons R^+ + BrHg(CN)_2^- \qquad (4)$$

Initial rate constants for reactions of (I) were calculated from initial rates of reaction according to Equation (2). Initial rate constants for several temperatures and the enthalpy ($\Delta H^{\ddagger}$) and entropy ($\Delta S^{\ddagger}$) of activation are presented in Table 1. In comparison to analogous mercuric cyanide-facilitated reactions of its 2-O-methyl analog (XI)[1], the enthalpy of activation (14.5 kcal mole^{-1}) for reactions of the 2-O-acetyl glucosyl bromide (I) is ca. 5 kcal mole^{-1} greater. The greater energy required for heterolysis of the carbon-bromine bond of (I) relative to (XI) reflects in part the inductive effect of the 2-O-acetyl substituent which decreases the electron density at C-1. The entropy of activation (-18.4 e.u.) for reactions of (I) is ca. 11 e.u. greater than $\Delta S^{\ddagger}$ for reactions of (XI)[1]. The reason for the greater $\Delta S^{\ddagger}$ for (I) is unknown. However, substituent changes within a series of similar compounds reacting by the same mechanism can effect changes in $\Delta S^{\ddagger}$ of this magnitude[18].

[Table 1 here]

Effect of Reactant Concentrations on the Product Distribution — The effect of variation in the reactant concentrations on the distributions of the initial and final products of reactions of the glucosyl bromide (I) are summarized in Table 2. The distribution of the final products was essentially independent of variation in any of the reactant concentrations. All of the final product mixtures were similar and contained a high proportion of β-glucoside ($n_{\beta} \geq 0.93$).

[Table 2 here]

The distribution of initial products was independent of the concentration of the glucosyl bromide (I) and $Hg(CN)_2$. However, the distribution of the initial products was significantly dependent on the concentration of cyclohexanol. As the alcohol concentration was increased, the initial mole

fraction of β-glucoside (IV) (n_β) increased while those of the α-glucoside (V) (n_α) and the orthoester (III) (n_{OE}) decreased.

Reaction Mechanism — The overall mechanism proposed to account for glucoside formation in mercuric cyanide-promoted reactions of the 2-O-acetyl-glucosyl bromide (I) with cyclohexanol is shown in Figure 6. The rate-determining step in the reaction of (I), heterolysis of the carbon-bromine bond assisted by $Hg(CN)_2$, results in formation of a shielded carbonium ion, probably an ion pair (XII). The ion pair can either react directly with cyclohexanol to form the 2-O-acetyl-β-D-glucoside (IV) or it can dissociate to form a free carbonium ion (XIII). The free carbonium ion can react with the alcohol to form the 2-O-acetyl-β- (IV) and -α-glucoside (V) or form the 1,2-dioxolenium ion (II) by intramolecular reaction of the C-2 acetoxy carbonyl oxygen atom with electron deficient C-1. Subsequent reaction of cyclohexanol with the 1,2-dioxolenium ion (II) results in formation of the orthoester (III). As the alcohol concentration is increased, the probability of it reacting with the ion pair (XII) before the ion pair can dissociate to the free carbonium ion (XIII) increases. Thus, as the alcohol concentration was increased (Table 2), the proportion of β-glucoside (IV) in the initial products increased, whereas the proportion of α-glucoside (V) and orthoester (III), which would be formed via the free glycosyl carboxonium ion (XIII), decreased.

[Fig. 6 here]

The fact that the α-glucoside (V) and the orthoester (V) are initial products of the reaction indicates that some of the ion pairs do dissociate to form free carbonium ions. Halide exchange [Equations (5) and (6)] could

$$\alpha\text{-ion pair} \underset{}{\overset{Br^-}{\rightleftharpoons}} \beta\text{-ion pair} \qquad (5)$$

$$\alpha\text{-glucosyl bromide} \overset{Br^-}{\rightleftharpoons} \beta\text{-glucosyl bromide} \qquad (6)$$

potentially account for formation of the α-glucoside (V)[5,6,19] and the orthoester (III)[20]. However, if halide exchange was totally responsible for formation of these compounds, the initial mole fractions of α-glucoside (V) (n_α) and the orthoester (III) (n_{OE}) in the products would be zero. This is definitely not the case (Table 2).

The orthoester subsequently forms glucosides (Figure 6), the reaction being very selective for formation of the 2-O-acetyl-β-glucoside (IV) under these conditions. Previous studies[10,11] indicate that acid-catalyzed glucoside formation from the orthoester (III) involves formation of a carbonium ion at C-1 concurrent with formation of a 2-O-(1-cyclohexoxy-1-hydroxy-ethyl) substituent (XIV, Figure 6). The alcohol reacts at C-1 to form glucosides, with formation of the β-anomer being preferred because of shielding by the departing orthoacid group. The orthoacid moiety at C-2 can yield either the 2-O-acetyl derivative of the glucoside or form cyclohexyl acetate leaving the hydroxyl group at C-2 unsubstituted[9,11]. However, the latter reaction must not be important under these reaction conditions since the 2-hydroxyglucosides (VI and VII) account for only a very small fraction of the glucosidic products.

The 2-O-acetyl substituent exerts its effect on the stereochemistry of the glucosyl bromide (I) reaction by selectively diverting the carbonium ion (XIII) from α-glucoside (V) formation to formation of the orthoester (III) which in turn selectively forms the β-glucoside (IV). The initial mole ratio of orthoester (III) to 2-O-acetyl-α-glucoside (V) was at least 5:1 in all of the reactions (Table 2). Preferential formation of the orthoester precursor, the 1,2-dioxolenium ion (II), relative to the α-glucoside (V) is probably due to the forced proximity of the carbonyl oxygen atom to the reaction center of the carbonium ion (XIII).

EXPERIMENTAL

Analytical Methods — M.p.s., elemental analyses, optical rotations, and p.m.r. spectra were determined as described previously[8]. T.l.c. was performed on silica gel G using methanolic sulfuric acid (5:1, wt) spray with charring for component detection.

The g.l.c. instrument was described previously[8]. Analyses were performed with: (A) 5% SE-52 on 60-80 mesh Chromosorb W (5 ft x 0.125 in o.d. stainless steel column); column, 160 → 220°C at 1° min^{-1}; N_2, 14 ml min^{-1}; injector, 205°C; and detector, 265°C; and (B) 5% SE-52 on 60-80 mesh Chromosorb W (10 ft x 0.125 in o.d. stainless steel column); column, 160°C; N_2, 60 ml min^{-1}; injector 205°C; and detector, 265°C.

Solvents and Reagents — Cyclohexanol[15], ethanol[21], methanol[21] were purified according to published procedures. Benzene, nitromethane, thiophenol, and mercuric cyanide were purified as described previously[1].

Compound Syntheses — General — 2-O-Acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide (I)[8], cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucopyranoside (IV)[8], cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranoside (V)[8], 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-α-D-glucopyranose (X)[9], and 3,4,6-tri-O-methyl-D-glucopyranose (XV)[9] were prepared as described elsewhere.

3,4,6-Tri-O-acetyl-1,2-O-[1-(exo-cyclohexoxy)ethylidene]-α-D-glucopyranose (XVI) — Compound (XVI) was prepared in 69% yield by reacting tetra-O-acetyl-α-D-glucopyranosyl bromide[22] with cyclohexanol in the presence of tetraethylammonium bromide as described for the preparation of 3,4,6-tri-O-acetyl-1,2-O-[1-(exo-ethoxy)ethylidene]-α-D-glucopyranose[9]. The pure product was obtained by crystallization from isopropyl ether containing a trace of pyridine

and had m.p. 82-83°C, $[\alpha]_D$ + 27.9° ($CHCl_3$) (Found: C, 56.1; H, 6.8. $C_{20}H_{30}O_9$ requires C, 55.8; H, 7.0%). The p.m.r. chemical shifts ($CDCl_3$) of the dioxolane 2-methyl protons [δ 1.73 p.p.m. (s)] and the anomeric proton [δ 5.69 p.p.m. (d, $J_{1,2}$ 5.2 Hz)] are indicative of the exo-cyclohexoxy configuration[20].

1,2-O-[1-(exo-cyclohexoxy)ethylidene]-3,4,6-tri-O-methyl-α-D-glucopyranose (III) — Compound (III) was prepared by methylation of the O-acetyl analog (XVI) with dimethyl sulfate as described for the preparation of 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-α-D-glucopyranose (X)[9]. The crude product (93% yield) was purified by fractional distillation under reduced pressure (ca. 0.05 mm Hg) through a 10 cm Vigreux column. The purified oil had $[\alpha]_D$ + 37.4° ($CHCl_3$) (Found: C, 59.0; H, 8.6. $C_{17}H_{30}O_7$ requires C, 58.9; H, 8.7%). P.m.r.: δ ($CDCl_3$) 1.68 (s, $CH_3 \cdot C$); 5.63 (d, $J_{1,2}$ 5.2 Hz, H-1); 4.37 (m, $J_{2,3}$ 3.1 Hz, H-2); 3.41, 3.45, and 3.48 (3 x MeO); and 1.0-2.0 p.p.m. (m, H-cyclohexyl).

Cyclohexyl 3,4,6-Tri-O-methyl-β-D-glucopyranoside (VI) — Cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucopyranoside (IV) was deacetylated with sodium methoxide in methanol[23]. The solution was deionized (Amberlite MB-3) and concentrated in vacuo to an oil. The product, purified by fractional distillation through a 10 cm Vigreux column under reduced pressure (ca. 0.1 mm Hg), crystallized during storage and had m.p. 48.5-50°C, $[\alpha]_D$ - 29.8° ($CHCl_3$) (Found: C, 58.9; H, 9.1. $C_{15}H_{28}O_6$ requires C, 59.2; H, 9.3%). P.m.r.: δ ($CDCl_3$) 4.30 (d, $J_{1,2}$ 6.5 Hz, H-1); 3.04 (s, OH-2); 3.40, 3.53, and 3.65 (3 x MeO); and 1.2-2.0 (m, H-cyclohexyl).

Cyclohexyl 3,4,6-Tri-O-methyl-α-D-glucopyranoside (VII) — Cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranoside (V) was deacetylated with sodium methoxide in methanol[23]. The solution was deionized (Amberlite MB-3)

and concentrated *in vacuo* to an oil which had $[\alpha]_D$ + 144 ($CHCl_3$) (Found: C, 59.0; H, 9.2. $C_{15}H_{28}O_6$ requires C, 59.2; H, 9.3%).

Ethyl 3,4,6-Tri-*O*-methyl-2-*O*-propanoyl-β-D-glucopyranoside (XVII) — Ethyl 3,4,6-tri-*O*-methyl-β-D-glucopyranoside[10] (2.0 g) was treated with propanoic anhydride-pyridine (12 ml; 1:2, vol) for 24 h. The solution was stirred with ice water for 0.5 h and extracted with chloroform (3 x 75 ml). The chloroform extracts were washed with 1N H_2SO_4 (100 ml), saturated $NaHCO_3$ (100 ml), and water (50 ml); dried ($CaCl_2$); and concentrated *in vacuo* to an oil (2.1 g, 93%) which was distilled under reduced pressure (*ca.* 0.05 mm Hg) in a Kontes short-path distillation apparatus. The distillate was crystallized from isopropyl ether and had m.p. 38-39°C, $[\alpha]_D$ - 20.5° ($CHCl_3$) (Found: C, 54.9; H, 8.5. $C_{14}H_{26}O_7$ requires C, 54.6; H, 8.4%).

Phenyl 2-*O*-Acetyl-3,4,6-tri-*O*-methyl-1-thio-β-D-glucopyranoside (XVIII) — 2-*O*-Acetyl-3,4,6-tri-*O*-methyl-α-D-glucopyranosyl bromide[9] (7.0 g) in chloroform (150 ml) was treated with thiophenol (54 g) in 1M methanolic sodium methoxide (250 ml). After 15 min the reaction was diluted with water (150 ml) and extracted with chloroform (3 x 150 ml). The extracts were washed with 10% Na_2CO_3 (3 x 250 ml) and water (250 ml), dried ($CaCl_2$), and concentrated *in vacuo* to an oil (7.2 g, 95%). The crude product was purified by chromatography on silica gel (Sargent-Welch, 60-200 mesh) using isopropyl ether as the eluent. Crystallization from petroleum ether (bp 60-110°C) yielded (XVIII); m.p. 68-69°C, $[\alpha]_D$ - 0.8° ($CHCl_3$) (Found C, 57.4; H, 6.6; S, 9.2. $C_{17}H_{24}O_6S$ requires C, 57.3; H, 6.8; S, 9.0%). P.m.r.: δ ($CDCl_3$) 4.58 (d, $J_{1,2}$ *ca.* 10 Hz, H-1) 4.83 (m, H-2), 2.12 (s, OAc), and 7.1-7.7 p.p.m. (m, SC_6H_5).

Reaction Initiation — Anhydrous conditions were imperative throughout the following procedures because of the sensitivity of the glucosyl bromide (I) and the orthoester (III) to hydrolysis. All glassware was dried at 180°C for 24 h and stored in a vacuum desiccator (P_2O_5). Solvent transfers and weighing of compounds were conducted in a dry atmosphere.

Mercuric cyanide was weighed into a 50-ml volumetric flask. Anhydrous nitromethane (35 ml) was pipetted into the volumetric flask, and the mercuric cyanide was dissolved by refluxing the nitromethane. Subsequently, nitromethane (10 ml) was distilled from the flask to azeotropically dry the system. The flask was allowed to cool and weighed to determine the amount of nitromethane used in the reaction. For reactions of the glucosyl bromide (I), cyclohexanol was then weighed into the volumetric flask. If the reactions were analyzed by g.l.c. only, the internal standard (XVII), Drierite, and mercuric oxide (when used) were also weighed into the cooled nitromethane. For the reaction of the orthoester (III), the orthoester, internal standard (XVII), and Drierite were weighed into the cooled nitromethane.

Anhydrous benzene (35 ml) was pipetted into a second 50-ml volumetric flask. Benzene (10 ml) was distilled from the flask to azeotropically dry the system. The flask was allowed to cool and weighed to determine the amount of benzene used in the reaction. For reactions of the glucosyl bromide (I), the bromide (I) was then weighed into the flask. If the reactions were analyzed by g.l.c. only, Drierite was also weighed into the cooled benzene. For the reaction of the orthoester (III), cyclohexanol, HBr, and Drierite were weighed into the cooled benzene.

The two volumetric flasks were allowed to thermally equilibrate in a bath at the desired reaction temperature for 30 min. A bent (45°) connecting

tube was placed between the flasks and the contents of the two flasks were mixed together. Time zero for the reaction was taken to be the point at which mixing was begun. A sampling chamber[24] was attached to the flask containing the reaction solution to reduce the possibility of contamination by water during sampling, and the flask was returned to the constant temperature bath.

Polarimetric Analysis — The equipment and procedures used for polarimetric analyses were described previously[1].

G.l.c. Analysis — Samples (5.0 ml) taken of glucosyl bromide (I) reactions as a function of time were pipetted into a solution (0.38 ml) of thiophenol in 0.5M methanolic sodium methoxide (1:10, vol) to quench the reaction by converting unreacted (I) to phenyl 2-O-acetyl-3,4,6-tri-O-methyl-1-thio-β-D-glucopyranoside (XVIII) and to stabilize any orthoester (III) present in the sample. Samples (5.0 ml) of completed reactions of (I) (minimum of 10 h reaction time) and samples (5.0 ml) of the orthoester (III) reaction were pipetted into triethylamine-toluene (2.0 ml; 3:7, vol). For reactions which were also analyzed by polarimetry the internal standard (XVI) was added to the sample prior to the work-up.

To differentiate between orthoester hydrolysis products [(VIII) and (IX)] formed deliberately in the analytical procedure[9] and (VIII) and (IX) resulting from hydrolysis of the glucosyl bromide and the orthoester during the reaction, each sample was analyzed by two procedures.

Procedure A: A portion (3.0 ml) of the sample was concentrated in vacuo to an oil and an aqueous solution of bromcresol purple indicator* (4 ml) was added. Sulfuric acid (N, 4 drops) was added and, after 3 min, 0.01N NaOH was added to

*Bromcresol purple indicator (1.3 ml; Harleco, 0.04% solution) was diluted with water (100 ml).

pH 5-7. Buffer (0.4 ml; 0.1M K_2HPO_4 and 0.1M KH_2PO_4) was added and the solution was concentrated *in vacuo* to an oil.

The sample was treated with pyridine-propanoic anhydride (*ca.* 2 ml; 1:1, vol) at room temperature with occasional swirling for 24 hr. Water (15 ml) was added and, after 15 min, the solution was extracted with chloroform (3 x 15 ml). The extracts were washed with 2N HCl in saturated NaCl (10 ml), N NaOH in 10% NaCl (10 ml), and water (10 ml). After each washing the aqueous phase was back-extracted with a comparable volume of chloroform. The chloroform solutions were then combined for the succeeding stage of the procedure. The resultant chloroform solution was concentrated *in vacuo* to an oil. If residual propanoic acid was noted, it was removed by adding several ml of water and reconcentrating. The sample was dissolved in chloroform and analyzed by g.l.c.

The 1-*O*-acetyl- and 2-*O*-acetyl-3,4,6-tri-*O*-methyl-D-glucopyranose [(VIII) and (IX), monopropionates] determined by this procedure resulted from both hydrolysis of the glucosyl bromide and orthoester during the reaction and deliberate hydrolysis of the orthoester in the analytical procedure.

G.l.c. conditions A were used to analyze all samples. However, when samples had been treated with thiophenol in methanolic sodium methoxide, it was necessary to analyze for the monopropionates of the hydrolysis products [(VIII) and (IX)] using conditions B. An extraneous compound originating from the thiophenol reagent had the same retention time as (VIII) and (IX) under conditions A.

G.l.c. retention times (min) using conditions A were: (XVII) 12.0, (VIII) and (IX) (monopropionates) 14.5, (XV) (dipropionate) 19.2, (V) 27.0, (IV) 29.9, (VII) (monopropionate) 32.9, (VI) (monopropionate) 35.4, and (XVIII) 42.1. Retention times of (VIII) and (IX) (monopropionates) and (XVII) were 11.8 and 9.4 min, respectively, using conditions B.

Procedure B: A portion (2.0 ml) of the sample was concentrated *in vacuo* to an oil and treated with acetic anhydride-pyridine (*ca.* 2 ml; 1:2, vol) at room temperature with occasional swirling for 24 h. Water (15 ml) was added and, after 15 min, the solution was extracted with chloroform (3 x 20 ml). The extracts were concentrated *in vacuo* to 1-2 ml and N HCl (15 ml) was added. The mixture was shaken for 5-10 min and then extracted with chloroform (3 x 15 ml). The extracts were washed with N NaOH in 10% NaCl (5 ml) and water (5 ml). After each washing the aqueous phase was back-extracted with chloroform (10 ml) and the chloroform solutions were combined for the succeeding step of the procedure. The final chloroform solution was concentrated *in vacuo* to an oil which was treated with propanoic anhydride-pyridine (*ca.* 2 ml; 1:2, vol) and analyzed by g.l.c. as described in Procedure A.

The monopropionates of (VIII) and (IX) determined by Procedure B result only from deliberate hydrolysis of the orthoester during the procedure.

The response factors required for quantitative g.l.c. were determined by subjecting synthetic mixtures of the necessary compounds to both analysis procedures.

P.m.r. Analysis — Anhydrous nitromethane (25 ml) was pipetted into a 50-ml volumetric flask containing $Hg(CN)_2$ (0.305 g). The mixture was refluxed to dissolve the $Hg(CN)_2$. Ethanol (0.806 g) was weighed into the cooled solution. The solution was transferred to a 250-ml volumetric flask and diluted with anhydrous nitromethane (75 ml). Anhydrous benzene (25 ml) was pipetted into a second 50-ml volumetric and the glucosyl bromide (I) (0.333 g) was weighed into the solvent. The solution was transferred to a second 250-ml volumetric flask and diluted with anhydrous benzene (75 ml). The above operations were performed in a dry atmosphere.

The two flasks were allowed to thermally equilibrate in a bath at 10°C for 1 h. The contents of the two flasks were mixed together and a sample of the solution was transferred to a water-jacketed polarimeter cell at 10°C. The remainder of the reaction solution was maintained in the bath. When the optical rotation of the reaction solution approached a constant value (ca. 90 min), thiophenol in 0.5M methanolic sodium methoxide (10 ml; 1:10, vol) was added to the reaction solution in the bath. The solution was concentrated to ca. 10 ml, filtered, washed with N NaOH (2 x 10 ml) and water (10 ml), and dried ($CaCl_2$). The solution was treated with pyridine (2 ml) and concentrated in vacuo to an oil. The oil was dissolved in $CDCl_3$ (ca. 0.4 ml) and analyzed by p.m.r.

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Table 1

Initial Rate Constants and Thermodynamic Functions of Activation

Temp (°C)	10^3 k (l mole^{-1} sec^{-1})[a]	$\Delta H^{\ddagger}$ (kcal mole^{-1})	$\Delta S^{\ddagger}$ (e.u.)[b]
25	14.1		
20	8.84	14.5	-18.4
15	5.81		
10	3.82		

[a] Average of duplicate determinations.

[b] Calculated for 20°C.

Table 2

Effect of Reactant Concentrations on Initial and Final Products at 10°C

Variable	ROH:RBr:$Hg(CN)_2$ Mole Ratio[a]	Initial Products[b] n_{OE}	Initial Products[b] n_β	Initial Products[b] n_α	Final Products[c,d] n_β	Final Products[c,d] n_α
Cyclohexanol (ROH)	7.5:1:1	0.53	0.39	0.08	0.93	0.07
	15:1:1	0.45	0.49	0.06	0.93	0.07
	22.5:1:1	0.36	0.60	0.04	0.93	0.07
	30:1:1	0.23	0.73	0.04	0.94	0.06
$Hg(CN)_2$	15:1:0.5	0.44	0.50	0.06	0.95	0.05
	15:1:2	0.45	0.50	0.05	0.93	0.07
Glucosyl bromide (RBr)	15:0.5:1[e]	0.47	0.48	0.05	0.94	0.06
	15:1:1	0.45	0.49	0.06	0.93	0.07

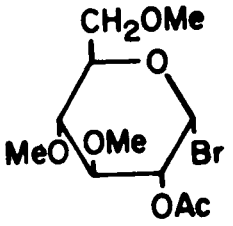
[a] 2-O-Acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide ca. 6×10^{-3}M. Benzene:nitromethane (1:1, vol) solvent.

[b] Mole fractions based on the orthoester and glucosidic products: n_{OE}, orthoester (III); n_β, 2-O-acetyl-β-glucoside (IV); and n_α, 2-O-acetyl-α-glucoside (V). The product distribution is corrected for hydrolysis products on the basis that the orthoester is the most readily hydrolyzed species[9]. Obtained by extrapolating g.l.c. analysis data to time zero.

[c] Product analyses after a minimum of 10 h reaction time.

[d] Mole fractions based on the glucosidic products; hydrolysis products (VIII) and (IX) accounted for 12-17% of the final products in the undesiccated reactions. The mole fraction n_β includes (IV) plus the 2-hydroxy-β-glucoside (VI) (0.0-0.02); n_α includes (V) plus the 2-hydroxy-α-glucoside (VII) (0.0-0.02).

[e] 2-O-Acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide ca. 3×10^{-3}M.



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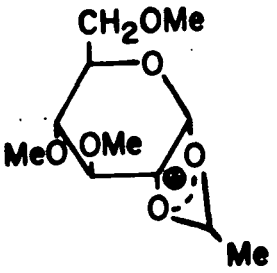

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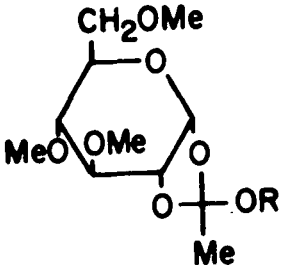
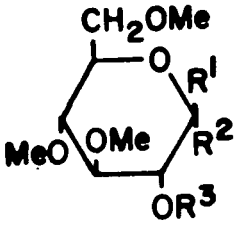


III: R = C_6H_{11}

X: R = Et



IV: $R^1 = OC_6H_{11}$, $R^2 = H$, $R^3 = Ac$

V: $R^1 = H$, $R^2 = OC_6H_{11}$, $R^3 = Ac$

VI: $R^1 = OC_6H_{11}$, $R^2 = H$, $R^3 = H$

VII: $R^1 = H$, $R^2 = OC_6H_{11}$, $R^3 = H$

VIII: $R^1 = H$, $R^2 = OAc$, $R^3 = H$

IX: $R^1 = H$, $R^2 = OH$, $R^3 = Ac$

XV: R^1, $R^2 = H$, OH, $R^3 = H$

XVII: $R^1 = OEt$, $R^2 = H$, $R^3 = COC_2H_5$

XVIII: $R^1 = SC_6H_5$, $R^2 = H$, $R^3 = Ac$

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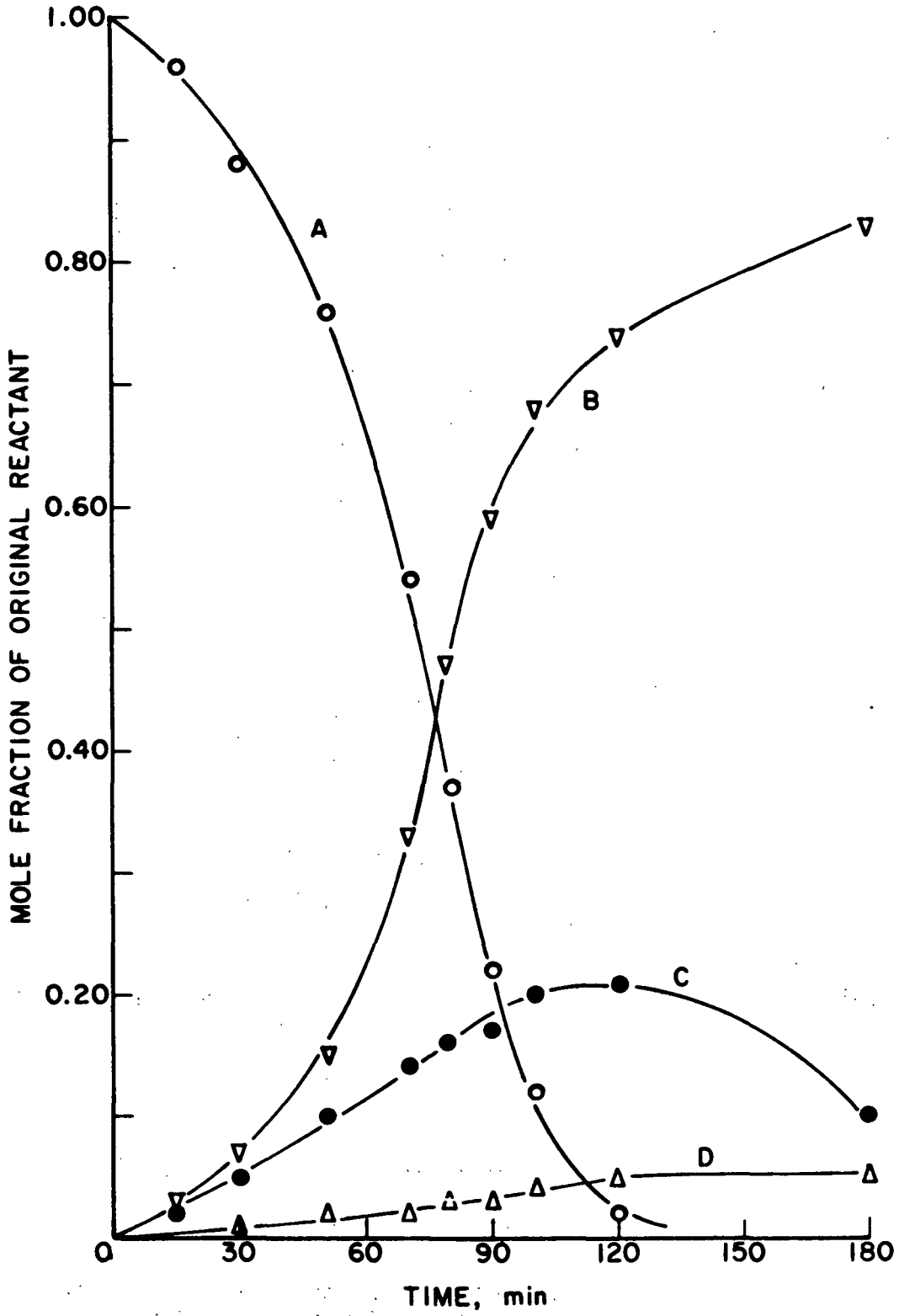

Figure 1. Reactant and product analyses for a reaction of the glucosyl bromide (I) (ca. 6.2×10^{-3}M) at 10°C and an initial reactant mole ratio of 1:1:15 (bromide (I):$Hg(CN)_2$:cyclohexanol): A, glucosyl bromide (I); B, cyclohexyl 2-O-acetyl-β-glucoside (IV); C, orthoester (III); D, cyclohexyl 2-O-acetyl-α-glucoside (V). Powdered Drierite was used as a desiccant.

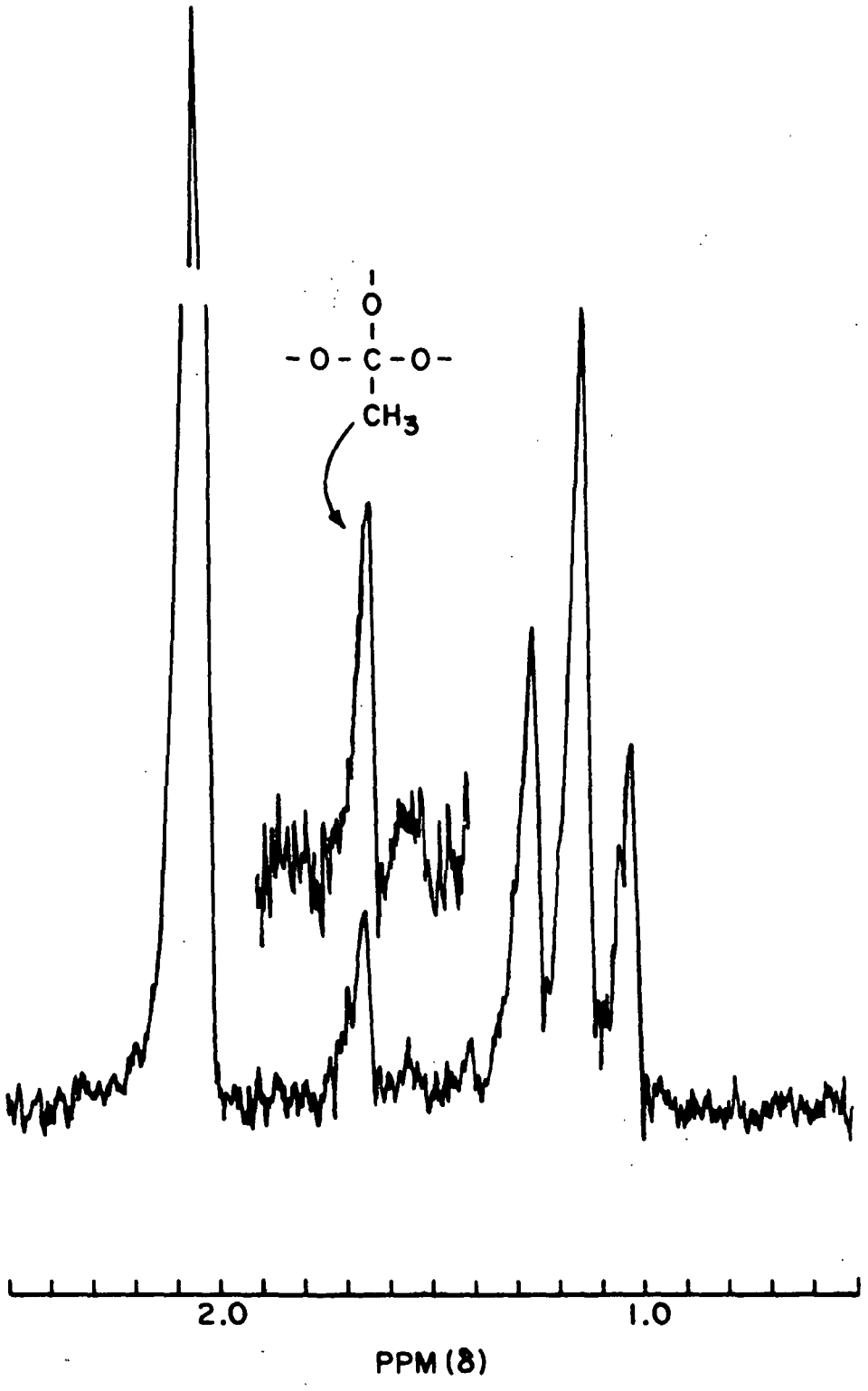

Figure 2. Partial p.m.r. spectrum ($CDCl_3$) of the reactant and products isolated from a mercuric cyanide-promoted reaction of the glucosyl bromide (I) with ethanol in benzene-nitromethane.

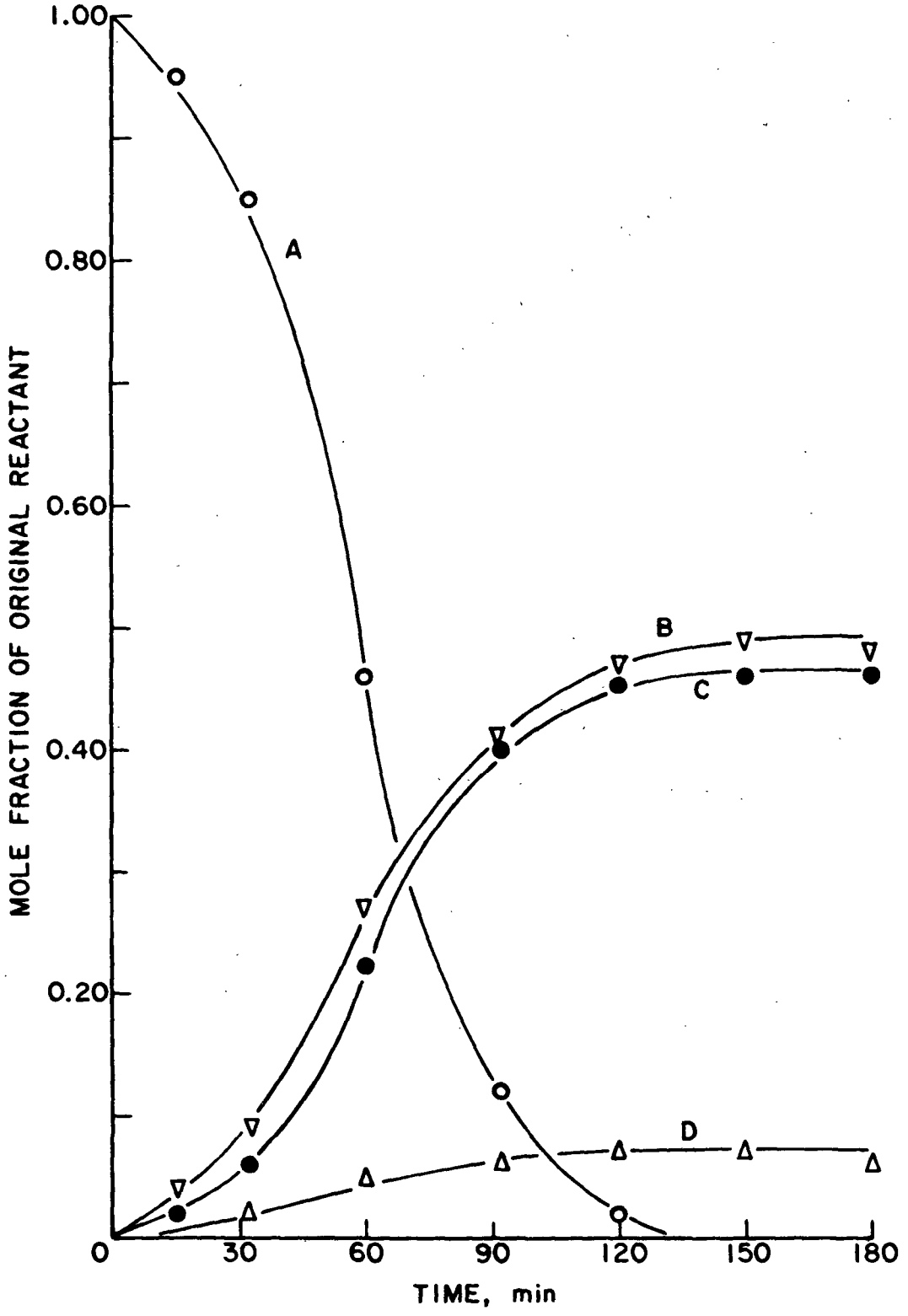

Figure 3. Reactant and product analyses for a mercuric oxide-buffered reaction of the glucosyl bromide (I) (ca. 5.4×10^{-3} M) at 10°C and an initial reactant mole ratio of 1:1:2:15 (bromide (I):$Hg(CN)_2$:HgO:cyclohexanol): A, glucosyl bromide (I); B, cyclohexyl 2-O-acetyl-β-glucoside (IV); C, orthoester (III); D, cyclohexyl 2-O-acetyl-α-glucoside (V). Powdered Drierite was used as a desiccant.

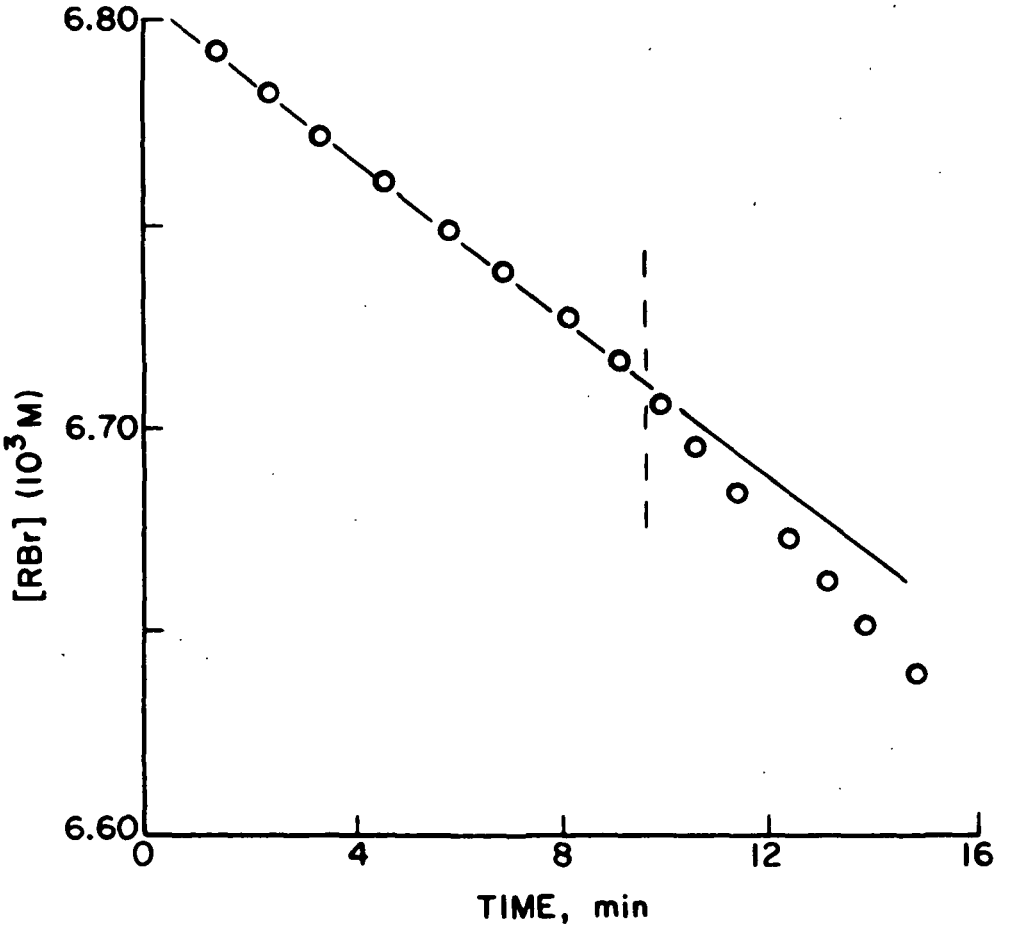

Figure 4. Initial reaction rate determination: 10°C; 2-O-acetyl-glucosyl bromide (I), 5.79×10^{-3}M; $Hg(CN)_2$, 6.10×10^{-3}M. Initial slope = $(d[RBr]/dt)_{t=0} = -1.45 \times 10^{-7}$ mol l^{-1} sec^{-1}.

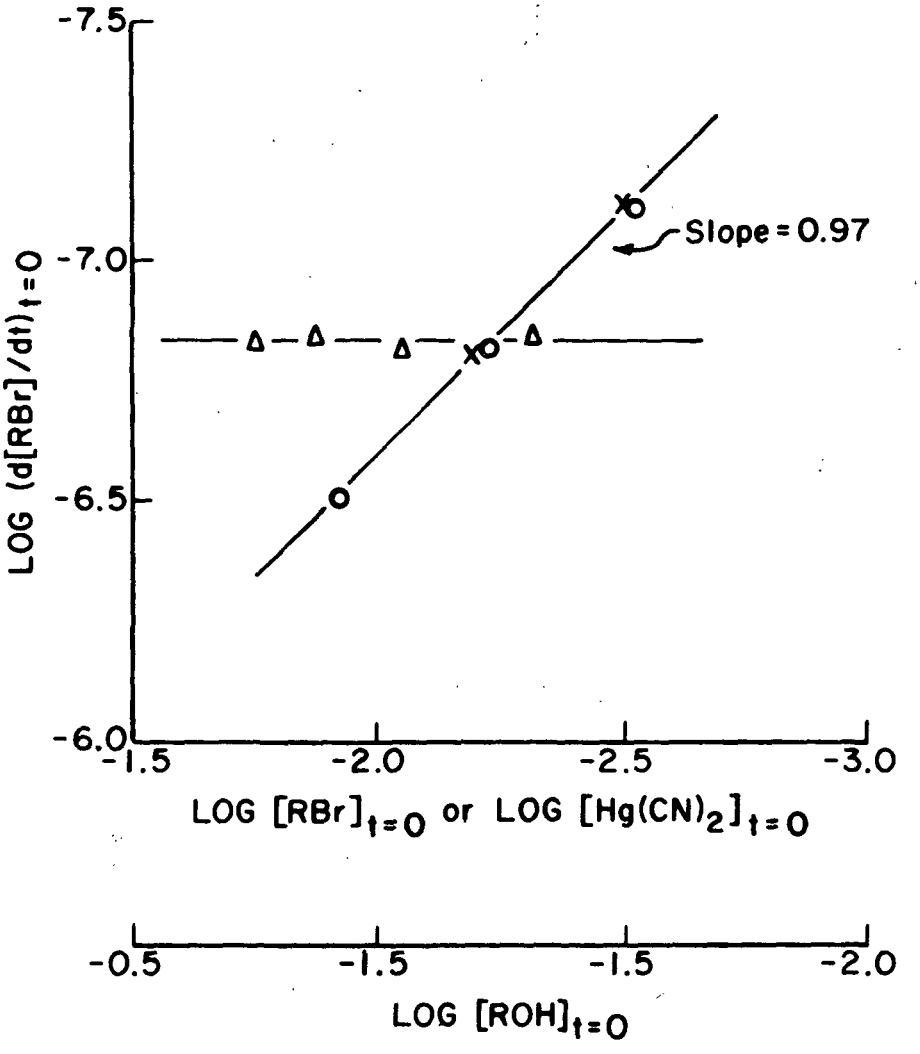

Figure 5. Reaction order determinations at 10°C. O - Glucosyl bromide (I); x - $Hg(CN)_2$; Δ - Cyclohexanol (ROH).

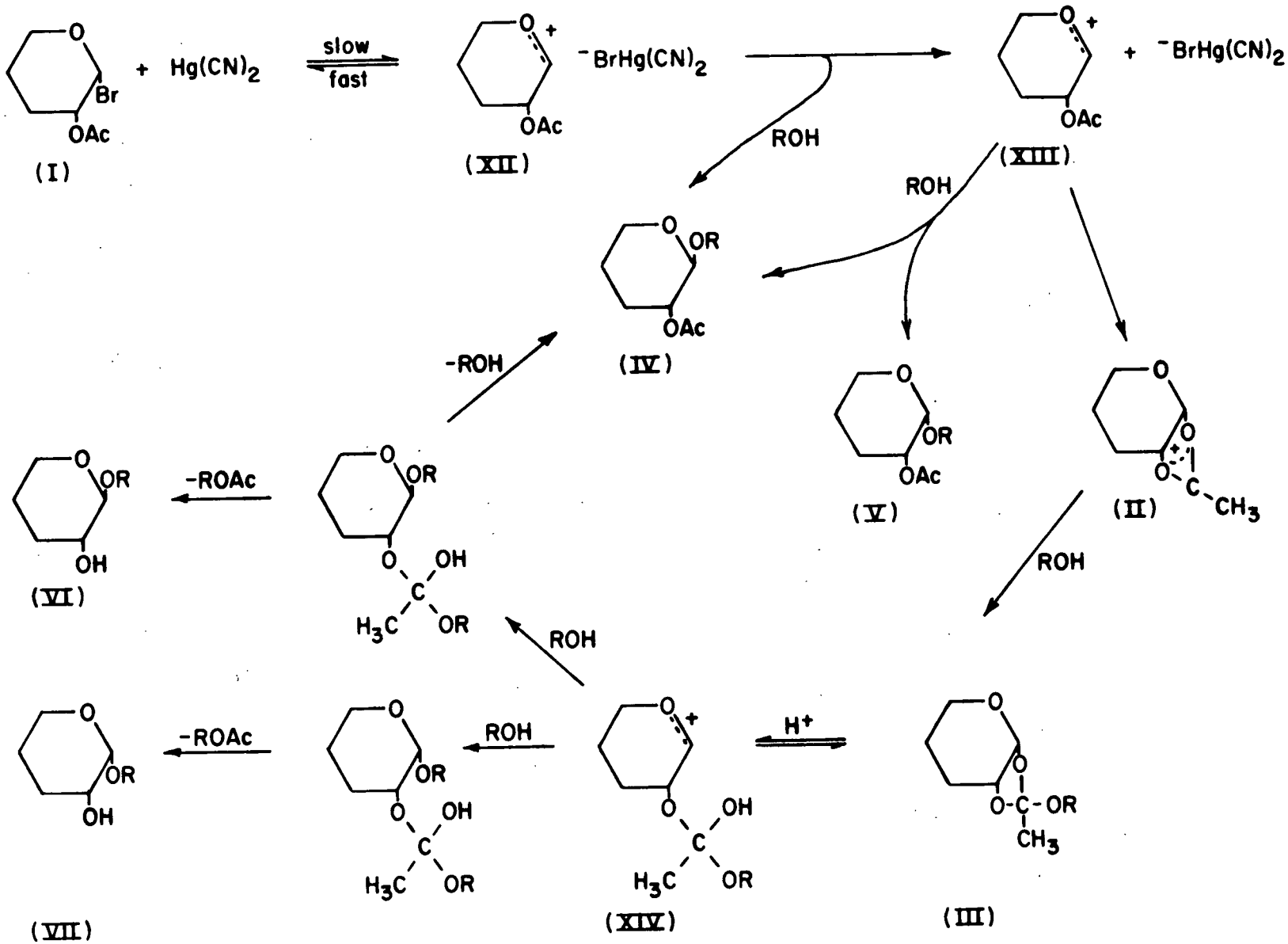

Figure 6. Proposed mechanism for glucoside formation in mercuric cyanide-promoted reactions of 2-O-acetyl-3,4,6-tri-O-methyl-α-D-gluco-pyranosyl bromide with cyclohexanol in benzene-nitromethane (3, 4, and 5 substituents of the pyranoid rings are not shown).